Remarkable and continued growth in the field of brain aging research has been fueled by a confluence of factors. Developments in molecular biology, imaging, and genetics coupled with the imperative caused by the aging of the population has created fertile ground for improved understanding of the interaction between brain function and behavior. Aging changes in neurochemical systems may account for the spectrum of cognitive and behavioral states of successfully aged persons, but may also contribute to enhanced vulnerability to depressive or dementing illness. In particular, the refinement of in vivo imaging approaches to investigating the structure and function of the aging brain has provided the opportunity to strengthen our knowledge of the biological substrate of the aging brain and neuropsychiatric disorders, and translate these into therapeutics.

Man (and woman) has long been fascinated with the workings of the human mind. Yet it is only recently that we have developed the tools to explore its biological underpinnings in the living state. The 1990 to 2000 interval was hailed as the Decade of the Brain. Advances in imaging, genetics, molecular biology, and pharmacology continue to advance our horizons in neuroscience research, but the scientific yield from these highly productive past 10 years will surely both usher in the developments of the future and guide the research achievements to important clinical applications. The gap between bench and bedside is narrower than ever and, importantly, there is increasing focus on not only lengthening the life span, but also improving the quality of mental and physical health in aging.

Anatomical and neurochemical systems affected by brain aging

Imaging structural brain changes in aging

Structural brain changes accompanying normal aging and neurodegenerative and psychiatric disorders may parallel and provide insight into the etiology of changes in cognition, mood, and motor function in the elderly. However, postmortem studies of brain morphology are plagued by artifacts caused by changes in hydration states just prior to death and tissue fixation. These studies are biased toward end-stage disease states and permit only retrospective correlations with measures of brain function and behavior. Magnetic resonance imaging (MRI) offers a means of assessing structural brain changes in vivo and provides the opportunity to evaluate the relationship of morphologic parameters to mood, neuropsychological dysfunction, and treatment response. It is well known from both imaging and autopsy series that cerebrospinal fluid (CSF) increases and cerebral volume reductions accompany normal human aging.1-8
Several studies have suggested that age-related volume loss tends to affect some brain regions more than others. Jernigan et al localized aging changes in brain volume to be most marked in the caudate nucleus, anterior diencephalic structures, association cortices, and mesial temporal structures, with no changes found in the thalamus and anterior cingulate cortex. Murphy et al also found significantly larger MRI-determined volume losses in the caudate and lentiform nuclei than in the cerebral hemispheres in normal elderly men. These authors speculated that this finding was in accord with motor abnormalities encountered in the elderly. Similarly, preferential reductions in the size of the hippocampal formation in normal aging have been shown to correlate with delayed memory performance. It is important to bear in mind that age-related cerebral volume loss is highly variable among individuals and further accelerated by coincident medical illness. Conversely, DeCarli et al showed that temporal lobe volumes did not change over a range of 19 to 92 years of age, when only successfully aged men were included.

Due to considerable intersubject variability of age-related structural brain changes, cross-sectional study designs provide limited information about the rates and influences on such alterations. In a unique effort to determine the annual rate of brain volume changes in the healthy elderly, the Baltimore Longitudinal Study of Normal Aging has followed 94 elders with five annual MRI assessments. Preliminary findings support substantial annual intrasubject whole-brain volume reductions estimated to average 5.5 mL, with 1.4 mL increases in total CSF volume.

Nonspecific foci of increased white matter signal may be observed by MRI in normal individuals of all ages, but clearly increase in frequency with age, particularly after age 60. Pathologic correlates also point to an ischemic basis for these lesions, and blood flow reductions have been reported in association with white matter hyperintensities. Yet, whether white matter hyperintensities are associated with diminished cognitive function in aging is still unsettled.

Although substantial improvements in image processing and quantitative methods have recently been made, there are conflicting results among the numerous structural MRI studies of the aging brain due to a number of factors. These include methodological differences in imaging data acquisition and analysis, small sample size, and selection bias, such as failure to control for cerebrovascular risk factors. Still, morphologic changes in the brain that accompany aging follow processes—often with substantial delay—that begin at the cellular level. For this reason, investigative techniques that reflect functional or physiologic brain changes are typically more sensitive approaches for identifying the earliest and potentially reversible changes of healthy or pathologic aging.

**Cell loss in normal aging**

It was widely accepted that substantial neuronal loss occurred during normal aging with values as high as 50% in some hippocampal subregions, and that this was likely to be responsible for age-related decline in memory. Most early neuropathological studies used measures of neuronal density rather than cell number as the basis for measurement of cell loss. However, with the more recent application of stereological techniques to this field, it has become clear that normal aging is not accompanied by significant global decline in neuronal number. Within the hippocampus and associated cortical regions, there is no significant cell loss in entorhinal cortex, CA1, or temporal cortex of the undemented elderly. Some age-related cell loss does occur in the dentate gyrus and...
subiculum. It is, therefore, not possible to account for memory deficits in the elderly in terms of cell loss alone. The substrate for such change is more likely to be related to disruption of important hippocampal circuits short of cell loss. Such changes include the presence of neurofibrillary tangles within the entorhinal cortex, synapse loss in the terminal zone of the perforant pathway of the dentate gyrus, changes to dendrites, disruption of long-term potentiation, and decreases in the expression of the N-methyl-D-aspartate (NMDA) receptor in the molecular layer of the dentate gyrus.

**Age-related alterations in brain metabolism and perfusion**

Functional imaging tools, such as positron emission tomography (PET), single-photon emission tomography (SPECT), Xe- or xenon-enhanced computed tomography (CT), and optical imaging have permitted in vivo evaluation of brain perfusion and metabolic measurements. Yet, whether generalized physiologic measures such as resting cerebral blood flow (CBF) are altered in normal aging remains a point of controversy. Using the Xe inhalation method, which suffers from particularly poor spatial resolution relative to other methods, several investigators have demonstrated a significant reduction in mean CBF throughout the adult life span. With PET, Leenders et al. similarly demonstrated a decline of 0.5%/year in CBF, cerebral blood volume (CBV), and cerebral metabolic rate of oxygen (CMRO₂) in cortical brain regions. Several other investigators have also observed aging declines in CMRO₂, with a milder influence of age on CBF and oxygen extraction. One important potential confound in many of these studies is the diluting influence of age-related cerebral volume loss on these measurements. Due to the limited spatial resolution of many functional imaging techniques, partial volume averaging of cortical signal with enlarged sulcal CSF spaces can result in underestimation of metabolic parameters in older subjects. Applying MRI-based partial volume correction to [¹⁵O]water PET data, Meltzer et al. recently demonstrated no reduction in cortical CBF in healthy aging. This work challenges the interpretation of older studies, which did not account for this source of artifact that may dilute metabolic measures in the elderly. Although resting CBF may be normal in the successfully aged individual, age effects on small arterioles may reduce the autoregulatory capacity of the cerebral vascular system to respond to vasodilatory challenge, thus diminishing the brain’s ability to compensate for changes in systemic perfusion pressure and perhaps enhancing its susceptibility to ischemic damage.

PET studies of brain glucose utilization have similarly demonstrated disagreement among reports as to whether brain function declines with age. In 1982, Kuhl et al. reported a gradual aging decline in the mean cerebral metabolic rate of glucose utilization (CMRglc). Later studies supported a regional preference for age-related reductions in brain glucose metabolism in the frontal lobes, which were most marked after age 60. Duara et al., however, found no relationship between age and regional CMRglc in healthy men. Large inter-subject variability in the neurobiologic effects of aging has been noted by several investigators. These reports, individually limited by small sample sizes, suggest that aging effects on brain function are likely highly variable, affected by structural brain changes and systemic factors, and may differ between “successful aging” and individuals with substantial medical burden.

**Alterations in neurotransmitter systems**

The functional integrity of several neurotransmitter systems is altered by the aging process. Characterizing the profile of normal aging changes in neurotransmitter-mediated synaptic processes is the foundation upon which we will come to decipher the biological basis of behavioral and mood alterations accompanying aging. Further, the potential interaction between age effects and neurochemical disturbances associated with neuropsychiatric disease states may influence the susceptibility of the elderly to certain neurobehavioral disorders. Our knowledge of the effect of age on neurotransmitter function is primarily inferred by postmortem studies, with limited and variable regional sampling of the brain, and by animal models, which may not appropriately represent human brain aging. In contrast to studies of pathological changes in aging, there are many problems associated with the biochemical study of neurotransmission in humans. These include the effects of postmortem delay, hypoxia, and drug treatment, as well as the fundamental point that the material is removed most often removed following a terminal illness, which may itself influence neurotransmission regardless of the age at which the patient died. The reader is referred to a comprehensive review of the subject by DeKosky and Palmer.
With the development of highly selective radioligands for neuroreceptors, transporters, and other markers of neuronal function, it is possible to study the effects of aging and disease on brain neurotransmitter systems in vivo with PET. This approach permits whole-brain quantitative imaging in well-characterized subjects, with the potential for obtaining longitudinal measures. Such work has demonstrated specific aging reductions in dopamine and serotonin (5-hydroxytryptamine [5-HT]) receptor subtypes (Figure 1).47-50 Interestingly, there is evidence that some neuroreceptors actually increase in density with age, a finding of note in the opiate system.51 PET techniques are desirable relative to neuroendocrine challenge studies, which lack spatial localizing information and physiologic specificity. However, the combination of PET with neuropharmacologic probes is a powerful technique for localizing and quantifying neurotransmitter-mediated function in aging and disease.

Cholinergic system

There is considerable evidence for a presynaptic cholinergic deficit during aging in many brain regions based on reductions in the enzyme responsible for the synthesis of acetylcholine, choline acetyltransferase (ChAT), in cortex and striatum (as reviewed Palmer and DeKosky52) and in acetylcholine synthesis in temporal cortex.53 Furthermore, there are decreases with age in both muscarinic and nicotinic cholinergic receptors.54 Using proton magnetic spectroscopy, Cohen et al55 demonstrated reductions in the uptake of circulating choline with advancing age. Selective imaging ligands for the cholinergic system have proved elusive. However, PET studies with the relatively nonselective cholinergic receptor ligands [11C]benztropine, [11C]tropanyl benzilate, and [11C]-N-methylpiperidyl benzilate (NMPB) have supported in vivo losses in muscarinic receptor density with age, although they disagree on the magnitude of the reductions.56-58 Also, modest reductions in cholinergic terminal density with aging have been demonstrated by SPECT imaging of the vesicular acetylcholine transporter [123I]iodobenzovesamicol.59

Monoaminergic systems

There is wide variation in the response of monoaminergic systems to aging. While postmortem studies show considerable loss of markers of the 5-HT system (5-HT, 5-HT1A, and 5-HT2A receptors), particularly in the neocortex, and of dopaminergic markers (dopamine, major metabolites, transporter, and receptors) in the striatum,
there is little evidence of change outside those regions or in markers of the noradrenergic system. The development of selective imaging ligands for the 5-HT and dopamine binding sites has allowed these systems to be further studied in humans in vivo.

PET studies confirm substantial aging reductions in specific binding to dopamine D₁ and D₂ receptors. Further, alterations in cognition and coordination of motor activity that frequently accompany aging have been shown to correlate with PET measures of dopamine receptor function. Aging losses of presynaptic dopamine transporter sites have also been demonstrated with PET and SPECT, suggesting that age affects the integrity of dopaminergic neuronal pathways. Recently developed PET ligands for several 5-HT receptor subtypes and the 5-HT transporter have facilitated in vivo imaging of this important neurotransmitter system, which is central to mood and sleep regulation. Marked widespread aging reductions in binding of the pharmacologically well-characterized 5-HT₂A receptor using [¹⁸F]altanserin and [¹⁸F]setoperone have been shown by several investigators. The magnitude of the inverse relationship between age and 5-HT₂A receptor binding supports the hypothesis that loss of serotonergic function in aging may contribute to the susceptibility of the elderly to alterations in mood and 5-HT–mediated behaviors. Intriguing preliminary evidence suggests gender differences in the effect of age on the 5-HT₁A receptor.

**Amino acid systems**

Glutamic acid decarboxylase, responsible for the synthesis of γ-vinyl γ-aminobutyric acid (GABA), declines with age in cortex, hippocampus, and striatum, while there is limited evidence for decreases in markers of the glutamatergic system (transporter and NMDA receptor). It is, however, difficult to assess the status of the presynaptic glutamatergic system since the neurotransmitter is a ubiquitous component of all cells. While no changes have been reported in [¹H]MK801 binding (to the ion channel) from middle age to old age, age-related changes in the ability of glutamate and glycine binding sites to influence binding within the channel have been observed. For example, the ability of glutamate and glycine to enhance [¹H]MK801 binding in the frontal cortex is reduced from a 44% increase in young adults to a 35% increase in 80- to 100-year-old humans. Furthermore, spermine stimulation of [¹H]MK801 binding via the polyamine site disappears by 80 years of age and zinc inhibition also declines with increased age. Reduction in binding to one or more sites on the NMDA receptor complex with age may reflect losses of the entire receptor complex, a selective loss of certain subunits, or both. There is some evidence from studies in mice that changes in receptor subunit composition occur with age and may form the basis for changes in the affinity of certain binding sites.

**Influence of gender on brain aging**

The profound impact of sex steroids on brain structure and function is evidenced by sexual dimorphisms in brain organization and development, which have been associated with gender-based differences in behavior and learning. Recent evidence of male–female differences in brain aging supports an ongoing dynamic relationship between sex steroids and neural structure and function. This includes work by Honeycutt et al., which demonstrates differential aging patterns for the morphology of mesial temporal structures, particularly the amygdala, in men and women. In vivo evidence of male–female differences in neuroreceptor distribution has been shown for 5-HT₂A receptors, and a specific age–gender interaction on 5-HT₁A receptors has recently been reported. Gender preferences for psychiatric disorders, particularly depressive illness, also support a biological underpinning for functional brain differences in men and women. Women clearly exhibit higher rates of depression in early and middle adulthood, with enhanced risk associated with surgical menopause and antiestrogen treatment for breast cancer. However, there is evidence for a narrowing of the gender gap in mood disorders in older middle adulthood, for which a neuroendocrine basis is speculated. Animal models demonstrating a positive effect of estrogen on memory task performance, particularly working memory, and the observation that normal hormonal cycling affects cognitive performance in women suggest a role for ovarian steroids in mediating cognitive function. However, variable outcomes have resulted from clinical investigations of hormone replacement therapy (HRT) and cognition in aging women. In a community-based study of over 700 postmenopausal women, Jacobs and colleagues noted higher cognitive measures in HRT users relative to nonusers. They also
found slight improvements in verbal memory performance over the follow-up interval. However, these findings were not independent of age and education level. Other investigators have reported no clear beneficial effect of estrogen replacement therapy on cognitive function, and no relationship between endogenous estrogen levels on cognitive test performance. Interestingly, an association between higher endogenous testosterone levels and cognitive performance has been noted in women. It has been further suggested that a lack of epidemiological evidence of gender differences in cognitive decline with aging argues against a link between estrogen deficiency and cognitive dysfunction. Research to date on male aging has been limited and the clinical relevance of the aging decline of testosterone levels in men is debated. Although androgens clearly play a role in brain development and sexual brain dimorphisms, central mechanisms for modulating human behavior are less well characterized (for a review, see reference 96). Androgen receptors are found in many brain regions with particular localization to the hippocampus, where, similar to estrogen, they modulate hyperpolarization of pyramidal cells in the CA1 region. In healthy young men, testosterone levels have been shown to correlate positively with spatial cognitive function and negatively with verbal performance. Beneficial effects on spatial cognitive function in men have been associated with an optimal level of testosterone, with deterioration of performance observed at both high and low levels. Although the concept of testosterone supplementation remains controversial, randomized, controlled trials of androgen replacement therapy in healthy older men have demonstrated enhanced spatial cognitive ability. Overall, the potential benefits of androgen replacement in elderly men appear to weigh favorably against minor potential added risks to cardiovascular and prostate health.

Late-life neuropsychiatric disorders

Depression

The association of evidence of disruption of structural brain integrity (e.g., white matter lesions) and late-life, particularly late-onset, depression further underscores the potential multiplicity of biological factors relevant to depressive illness occurring in the elderly. The correlation between white matter hyperintensities and hypertension and/or atherosclerotic disease may parallel and provide insight into the role of cerebral ischemia in the etiology of late-life depression, since an increased prevalence of both cerebrovascular risk factors and white matter hyperintensities has been observed in elderly depressed patients, particularly those with a late onset of their disease. These observations have led some investigators to postulate an MRI-defined vascular or atherosclerotic form of depression, which supports a strong link between aging and biological factors in depression occurring in the elderly. Also, evidence for serotonergic control of the regulation of CBF and the potential influence of age on this regulatory mechanism suggest an interaction—although as yet ill-defined—between disturbances in serotonergic function and risk of cerebral ischemic injury. Depression has been widely attributed to deficient 5-HT neurotransmission. In the unique setting of geriatric depression, age-related alterations in the 5-HT system may perturb its functional integrity and thus potentially contribute to the high prevalence and distinct character of depression in late life. Postmortem studies have reported conflicting findings of 5-HT receptor status in suicide victims. In a small group of elderly nonsuicide depressed patients, reductions in binding to 5-HT<sub>2A</sub>, but not to 5-HT<sub>1A</sub>, sites in temporal, frontal, and parietal cortex were reported using membranes. Using autoradiographic techniques, the density (B<sub>max</sub>) for the 5-HT<sub>1A</sub> receptor was reduced by approximately 40% in the superficial layers of frontal cortex (Brodmann area 9) from patients undergoing surgery for intractable depression. It is also worth noting that there was a 30% to 40% reduction in the concentration of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in the ventricular CSF of these depressed patients, underlining the possible relationship between disturbances of serotonergic neurotransmission and depressive symptoms.

Evaluation of serotonergic function through imaging techniques has offered a unique approach to evaluating the heterogeneity of depression in the elderly. In an attempt to assign neurochemical specificity to the blood flow and metabolic disturbances reported in depression, fluoroexoxyglucose (FDG) PET coupled with the 5-HT-releasing agent d-fenfluramine provided indirect yet in vivo evidence of serotonergic dysfunction in the prefrontal cortex in depressed patients, who exhibited a blunted response relative to healthy controls. With the subse-
sequent development of selective imaging agents for serotonergic receptor sites, it became possible to quantify central 5-HT binding in depressed patients. Of particular interest are the 5-HT2A and 5-HT1A receptors and the 5-HT transporter, which are all heavily implicated in the antidepressant response (Figure 2). There are few published studies to date of serotonergic PET imaging in mood disorders and fewer conducted in elderly patients. Biver et al demonstrated a significant reduction in the binding of [18F]altanserin to right orbitofrontal 5-HT2A receptors in a group of mid-life depressed subjects. However, this agent failed to show a change in 5-HT2A receptor binding in late-life depression. Drevets et al recently reported reductions in 5-HT1A binding of [11C]WAY100635 to mesiotemporal and brainstem raphe areas in familial mood disorders including bipolar depressives. Whether this finding is generalizable to nonfamilial forms of mood disorders and late-life depression is yet uncertain. The capability to selectively evaluate neurotransmitter binding sites in vivo will likely continue to be a valuable tool for determining the biological underpinnings of late-life depression and sources of treatment response variability among patients.

Alzheimer’s disease: breaking the disease barrier

Alzheimer’s disease (AD), the most common form of dementia, has enormous and growing public health significance. A disease of aging, the financial and social burdens of AD are compounded by recent and continued increases in the average life span. It has been estimated that the prevalence of AD will continue to climb at a rapid rate, with an expected quadrupling of cases in the United States over the next 50 years. Thus, the need for developing early diagnostic markers to complement new therapeutic approaches is more acute than ever before. Indeed, a modest goal of instituting treatment that could delay disease onset by just 2 years would profoundly impact these projections, resulting in 2 million fewer cases by 2050.

**Biological basis of Alzheimer’s disease**

Cell death and histopathological changes affecting a number of neuronal systems are considered to result in the development of the typical symptomatology of AD characterized by gross and progressive impairments of cognitive function. The histopathological features are intracellular neurofibrillary tangles formed from a hyperphosphorylated form of the microtubule-associated protein, tau, and extracellular deposits of a 40/42 amino acid peptide, Aβ (derived from amyloid precursor protein [APP]), often in the form of senile or neuritic plaques. Plaques, tangles, and cell loss have a characteristic regional and temporal distribution in the AD brain, affecting entorhinal, hippocampal, and temporal cortical structures first and frontal and parietal cortices later in the disease process, while sparing primary sensory and primary motor areas. Indeed, this pathology is reflected in the characteristic regional pattern of blood flow and metabolic disturbances demonstrated by PET or SPECT imaging in early AD. Evidence from biochemical studies also indicates that certain subcortical structures, including the nucleus basalis of Meynert and the dorsal raphe are also affected early in the disease. Most cases of AD are considered to be sporadic and therefore of unknown cause; however, there are a number of autosomal dominant mutations (Table I) that

| Chromosome | Gene | Number of mutations | Age of onset (years) | Proportion cases |
|------------|------|---------------------|---------------------|-----------------|
| 21         | APP  | 9                   | 50s                 | <0.5%           |
| 14         | P51  | >40                 | 40s                 | 2%-4%           |
| 1          | P52  | 2                   | 50s                 | <0.5%           |

**Table I. Genes causing Alzheimer’s disease (AD).**
cause AD and several genetic risk factors, the best known of which is apolipoprotein E (apo E) ε4 polymorphism, the presence of which carries an approximately sixfold greater risk of developing AD. While the disease-causing mechanism behind apo E remains controversial, most studies indicate that mutations in the genes APP, presenilin 1 (PS1), and presenilin 2 (PS2) alter the metabolism of APP so as to favor production of a long form of Aβ (Aβ 1-42) (see, for example, reference 134).

Neurotransmitter changes in Alzheimer’s disease

The majority of biochemical studies of AD have relied on information derived from postmortem brain, which typically represents the late stage of the disease (8-10 years after onset of symptoms). In these studies, there is considerable evidence for multiple neurotransmitter abnormalities affecting many brain regions. However, investigations of biopsy tissue taken from AD patients 3 to 5 years (on average) after the onset of symptoms indicate that a selective neurotransmitter pathology occurs early in the course of the disease.

Acetylcholine. Changes affecting many aspects of the cholinergic system in patients with AD have been reported since the initial discovery of deficits in ChAT activity in postmortem brains. In biopsy samples from AD patients, presynaptic markers of the cholinergic system were also uniformly reduced. Thus, ChAT activity, choline uptake, and acetylcholine synthesis are all reduced to between 30% and 60% of control values. The clinical correlate of this cholinergic deficit in AD was until recently considered to be cognitive dysfunction. Such a conclusion was supported by clinicopathological studies in AD and parallel experiments in nonhuman primates or rodents, which demonstrated disruptive effects of basal forebrain cholinergic lesions on cognitive functions. Furthermore, cholinergic deficits in AD occur to the greatest extent in cortical areas primarily concerned with memory and cognition: the hippocampus, adjacent temporal lobe regions, and selected frontal areas. Such studies led to the “cholinergic hypothesis of geriatric memory dysfunction.” On the basis of the above evidence, neocortical cholinergic innervation appears to be lost at an early stage of the disease and this is supported by a recent study where the cholinergic deficit (reduced ChAT activity) has been related to Braak staging. Braak stages I and II are considered to represent the earliest presentation of AD with neurofibrillary tangles in entorhinal cortex, and a 20% to 30% loss in ChAT activity was reported in brains from patients at these stages of AD. However, another study using the Clinical Dementia Rating (CDR) scale suggests that the greatest reduction in markers of the cholinergic system occurs between moderate (CDR 2.0) and severe (CDR 5.0) disease with little change between nondemented and the mild stage (CDR 0-2).

There has been a recent shift of emphasis regarding the clinical significance of cholinergic deficits. Noncognitive or neuropsychiatric, in addition to cognitive, symptoms also appear to have a cholinergic component. For example, visual hallucinations relate to neocortical cholinergic deficits, such deficits (eg, loss of ChAT) being greater in dementia with Lewy bodies (DLB), where hallucinations are common, than in AD, where they are less common. Reductions in cortical ChAT activity in patients with dementia, in addition to correlating with cognitive decline, are also related to overactivity and aggressive behavior.

Glutamate. Although neurochemical studies of glutamate neurotransmission have failed to demonstrate extensive alterations, this may be related to the difficulty in distinguishing the transmitter pool of glutamate from the metabolic pool. Nevertheless, glutamate concentration was reduced by 14% in temporal lobe biopsy samples and by 86% in the terminal zone of the perforant pathway at autopsy of AD patients. Uptake of D-aspartate, a putative marker of glutamatergic nerve endings, is also reduced in many cortical areas in the AD brain. In addition, loss of synapses and pyramidal cell perikarya (both considered to be markers of glutamatergic neurons) from the neocortex of AD patients correlate with measures of cognitive decline. Thus, additional factors other than impaired cholinergic function are likely to contribute to cognitive impairment in AD. However, it is important to remember that glutamatergic neurons of the neocortex and hippocampus are influenced by acetylcholine through nicotinic and muscarinic receptors. Thus, treatment of patients with cholinomimetics is likely to increase glutamatergic function.

Other neurotransmitters. In biopsy samples from AD patients, some noradrenergic markers are affected,
whereas markers for dopamine, GABA or somatostatin are not altered. When postmortem studies of AD brain are considered many neurotransmitter systems, including GABA and somatostatin, are involved or are affected to a greater extent. Changes in serotonergic neurotransmission seen at biopsy, postmortem, and recently in vivo may be linked to the behavioral disturbances of AD, such as depression, rather than cognitive dysfunction. For example, patients with AD who were also depressed had lower numbers of serotonin reuptake sites in the neocortex than AD patients without this symptom. Furthermore, both reduced serotonergic and increased noradrenergic activities and sensitivity have been linked to aggressive behavior.

**Neurotransmitter receptors.** The majority of neurotransmitter receptors appear to be unaffected in AD; however, studies have demonstrated a reduced numbers of nicotinic and muscarinic (M2) acetylcholine receptors, some of which are considered to be located on presynaptic cholinergic terminals. The M1 subtype is unchanged, but the coupling of the receptor to its G-protein may be impaired. A highly consistent receptor abnormality in AD is the loss of the nicotinic receptor, which appears to primarily reflect loss of the α4-containing subtype (generally associated with α2), as opposed to α3 or α7 subtypes. Immunohistochemically, loss of α4 and α2 reactive fibers has been observed in temporal cortex, associated with reactive neuropil threads, tangles, and plaques.

**Links between neurotransmission and neuropathology**

There is increasing evidence that various neurotransmitter systems are capable of influencing the metabolism of APP, favoring nonamyloidogenic processing. In particular, stimulation of muscarinic M1 receptors increases APP secretion, while decreasing β-amyloid production. These results suggest that compounds developed for symptomatic treatment may have a serendipitous effect on the continuing emergence of pathology by reducing the production of Aβ.

Cholinergic neurotransmission may be a specific target for Aβ, since it has been shown to reduce both choline uptake and acetylcholine release in vitro. Furthermore, Aβ is reported to bind with high affinity to the α7 subtype of the nicotinic receptor, suggesting that cholinergic function through this receptor may be compromised because of high levels of (soluble) peptide in AD brains.

**Translation of discoveries into therapeutics**

Biochemical studies in AD have generated a large number of therapeutic strategies for AD, many of which have been tested in same-scale, inconclusive studies. Only a few strategies have gone on to full-scale clinical trials. The best known of these is related to the cholinergic deficit. Moreover, while there are a number of rational approaches, including precursor loading and the use of muscarinic or nicotinic agonists, the use of acetylcholinesterase inhibitors (AChE-Is) is the most well-developed approach to the treatment of AD to date. Tacrine underwent large-scale clinical studies and clearly established the benefits of AChE-I treatment in patients with a diagnosis of probable AD. Statistically significant, dose-related improvements on objective performance-based tests of cognition, clinician- and caregiver-rated global evaluations of patient well-being, and also quality of life measures have been reported. Tacrine was subsequently approved for use in some, but not all, countries. Adverse side effects, including raised liver enzymes, have limited the use of this compound. Further AChE-Is have been developed including donepezil, rivastigmine, metrifonate, and galantamine. Such compounds demonstrate a clinical effect and magnitude of benefit of at least that reported for tacrine, but with a more favorable clinical profile including fewer and less serious side effects. Furthermore, evidence is emerging from clinical trials of cholinomimetics that such drugs may improve the abnormal noncognitive, behavioral symptoms of AD. The cholinesterase inhibitors phystigmine, tacrine, rivastigmine, and metrifonate have variously been reported in controlled trials to decrease psychoses (hallucinations and delusions), agitation, apathy, anxiety, disinhibition, pacing and aberrant motor behavior, and lack of cooperation in AD.

**Future directions: merging technologies**

Investigational neuropharmacologic techniques comprise a powerful and complementary collection of
research tools for studying the effects of aging and disease on regional and specific measures of brain function. These have allowed us to characterize both the normal neurochemical changes that accompany successful aging and the accelerated or aberrant alterations seen in neuropsychiatric and behavioral dysfunction. Future work will carry the findings of the past decade into the realm of intervention. Advancements in structural and functional imaging naturally complement those in molecular neurobiology and genetics, but we are just beginning to realize their potential combined power. For example, the recent availability of animal PET scanners presents the opportunity for the in vivo study of genetic models of disease, such as AD. Further, neuropharmacologic approaches to cognitive enhancement and slowing of dementia progression may be evaluated and monitored by imaging strategies. Indeed, the challenges posed by an increasingly aged population in industrialized nations are formidable, but may best be met by the combined application of developing technologies.

Figure 3. Schematic diagram of a neuron representing (A) alterations in neurotransmission in Alzheimer’s disease and (B) the hypothetical mode of action of acetylcholinesterase inhibitors. ACh, acetylcholine; AChE, acetylcholinesterase; Glu, glutamate; mAChR, ACh muscarinic receptor; nAChR, ACh nicotinic receptor; sAPPα, the alpha secretory product of amyloid precursor protein; Aβ, β-amyloid protein.

Reproduced from reference 166: Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer’s disease: a review of progress. J Neural Neurosurg Psychiatry. 1999;66:137-147. Copyright © 1999, Journal of Neurology, Neurosurgery, and Psychiatry.
La investigación sobre el envejecimiento cerebral hacia finales del siglo XX: desde la experimentación a la clínica

El notable y continuo crecimiento en el campo de la investigación sobre el envejecimiento cerebral ha sido incentivado por una confluencia de factores. El desarrollo de la biología molecular, de las técnicas de imágenes y de la genética, en conjunto con la exigencia determinada por el envejecimiento de la población han creado un terreno fértil para mejorar la comprensión acerca de la interacción entre la función cerebral y la conducta. Los cambios que produce el envejecimiento en los sistemas neuroquímicos pueden explicar el espectro de estados cognitivos y conductuales de personas de edad avanzada que han sido exitosas, pero también pueden contribuir a incrementar la vulnerabilidad a enfermedades degenerativas o demenciales. En particular, el refinamiento de las técnicas de imágenes in vivo que permiten investigar la estructura y función del cerebro que envejece ha dado la oportunidad de fortalecer nuestro conocimiento acerca del sustrato biológico del envejecimiento cerebral y de los trastornos neuropsiquiátricos, y traducir este conocimiento en terapias.

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La recherche sur le vieillissement cérébral à la fin du XXe siècle : de l’expérimentation à la clinique

Un ensemble de facteurs convergents a contribué au développement remarquable et constant de la recherche sur le vieillissement cérébral. C’est ainsi que les avancées de la biologie moléculaire, de l’imagerie et de la génétique tout autant que les impératifs liés au vieillissement inéluctable de la population ont créé un terrain propice à la recherche d’une meilleure compréhension de l’interaction entre la fonction cérébrale et le comportement. Si les modifications des systèmes neurochimiques dues à l’âge peuvent expliquer l’éventail des états cognitifs et comportementaux de patients qui ont bien vieilli, elles peuvent aussi contribuer à une augmentation de la vulnérabilité aux maladies dépressives ou dementielles. Les perfectionnements des méthodes utilisant l’imagerie in vivo pour analyser la structure et la fonction du cerveau vieillissant ont permis de consolider nos connaissances sur le substrat biologique du cerveau vieillissant et les désordres neuropsychiatriques et de traduire celles-ci sous forme de thérapeutiques.
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