Alzheimer's Disease

Although a disease-altering treatment has yet to be found, our understanding of Alzheimer's disease (AD) genetics and neurobiology has increased exponentially over the past few decades, as has our ability to detect Alzheimer's pathology using various biomarkers. In this chapter, we will review the genetic, pathological, and behavioral features of Alzheimer's disease and discuss how the use of biomarkers for the detection of AD has potentially opened up new avenues for the prevention (or possible reversal) of AD. Given the current absence of an effective pharmacological treatment, we will also describe how lifestyle may impact one's risk for developing AD and review potential strategies for reducing AD risk as well as reviewing currently available treatments aimed at ameliorating some of the symptoms of AD. For strategies to ameliorate some of the secondary behavioral symptoms often associated with Alzheimer's disease and other dementias, the reader is directed to Chapter 5.

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The Cost of Alzheimer's Disease

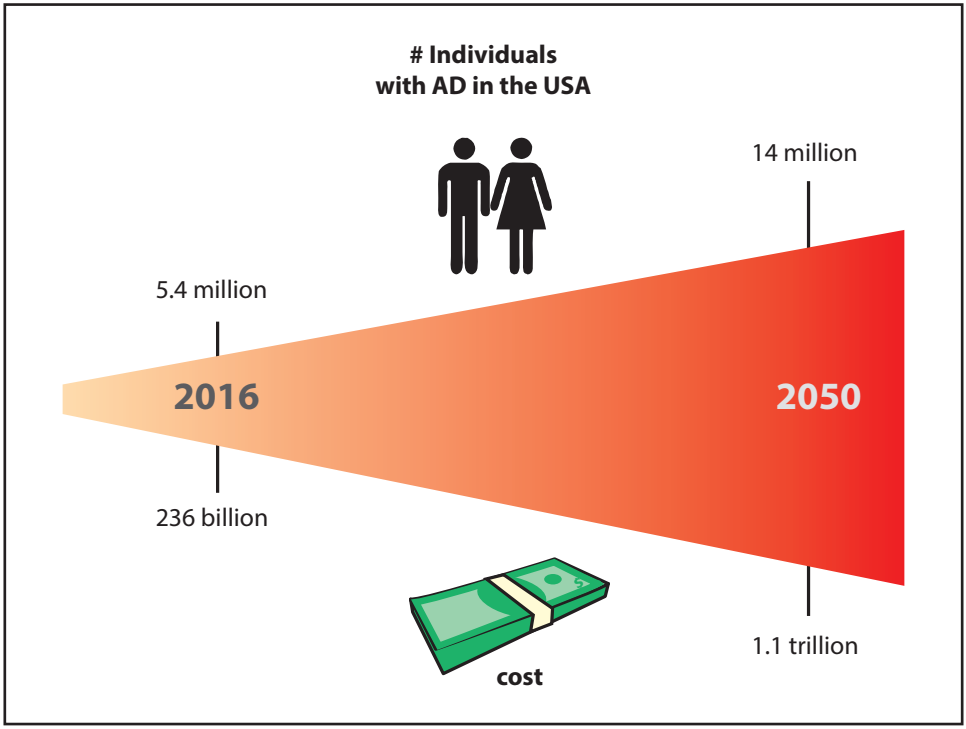

FIGURE 1.1. Alzheimer's disease (AD), the most common cause of dementia, is arguably the most devastating age-related disorder, with profound consequences to patients, family members, caregivers, and the economy. The latest data released by the Alzheimer's Association indicates that 5.4 million Americans presently have AD, costing the US approximately $236 billion annually. There is no cure for AD, and if no effective treatment is found by 2050, 14 million individuals will have AD—at an alarming annual cost of $1.1 trillion (Alzheimer's Association, 2017; Wimo et al, 2017).

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Alzheimer's Disease Pathology

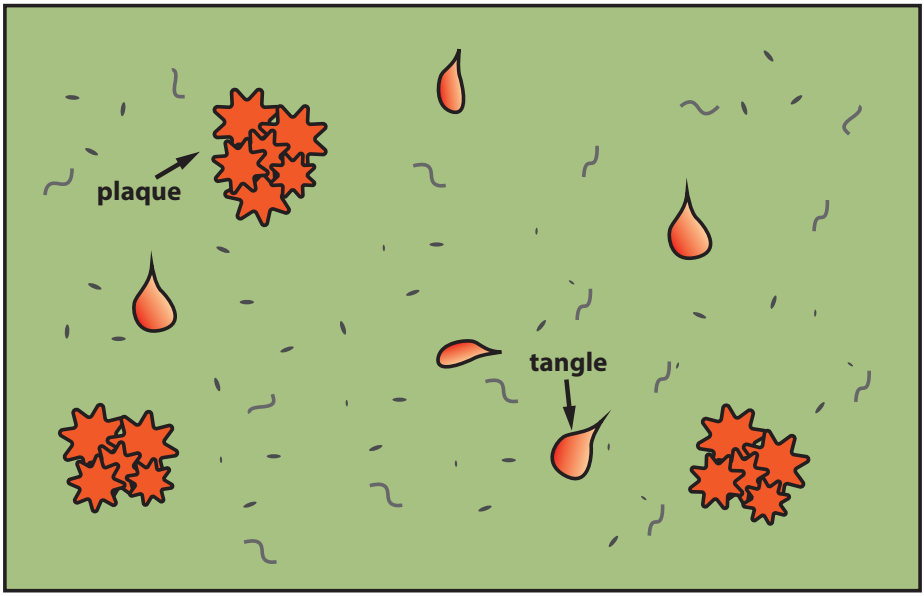

FIGURE 1.2. There are three major pathological hallmarks seen in the AD brain: plaques composed of the amyloid beta (Aβ) protein, neurofibrillary tangles (comprised of hyperphosphorylated tau protein), and substantial neuronal cell loss (Dugger and Dickson, 2017).

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Progression of Alzheimer's Disease Pathology

Phase/Stage	Thal Phases of Amyloid Pathology	Braak Stages of Tau Pathology
1 and 2	neocortex and hippocampus	entorhinal cortices
3	striatum	hippocampus
4	brainstem	limbic cortices
5/6	cerebellum	neocortex

FIGURE 1.3. In the AD brain, Aβ and tau pathology and neurodegeneration typically progress according to slightly different patterns. In line with the Thal phases of amyloid progression, Aβ pathology usually presents first in the hippocampus and neocortex and progresses ultimately to brainstem and cerebellum. Conversely, tau pathology typically begins in the transentorhinal cortices and progresses (according to Braak staging) to multimodal association cortices. Neurodegeneration of the AD brain affects various areas that correlate with pathology including cortex, hippocampus, amygdala, basal forebrain, and brainstem. However, not all cases of AD (perhaps as many as 20%) have AD pathology that follows these typical pathological patterns (Dugger and Dickson, 2017; Hinz and Geschwind, 2017).

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Amyloid Precursor Protein

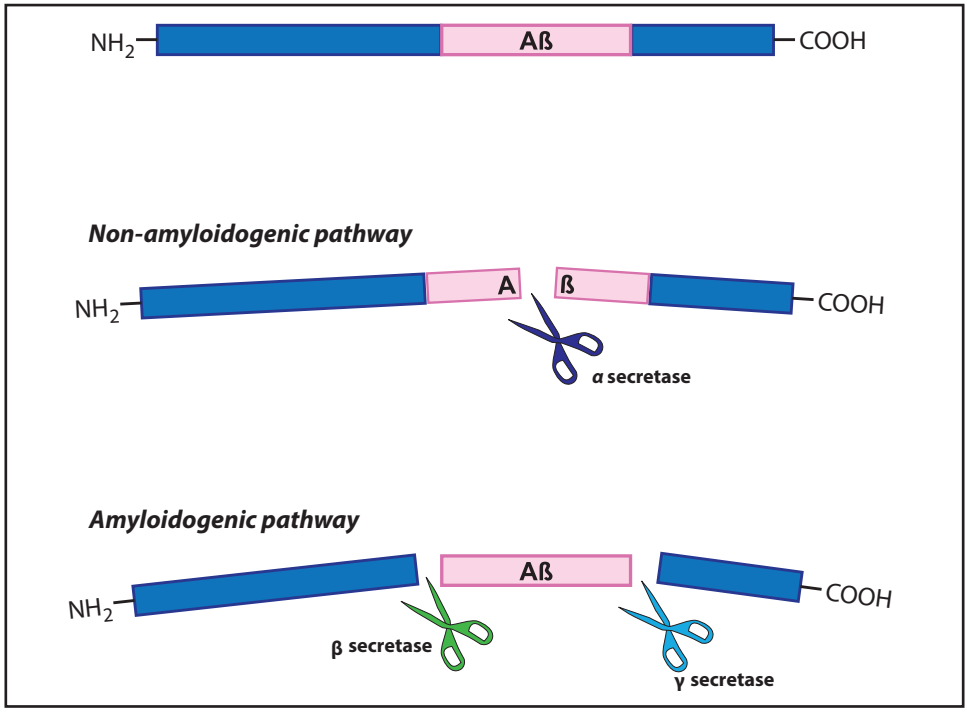

FIGURE 1.4. The Aβ protein is cut from a larger protein called the amyloid precursor protein (APP). There are two cleavage pathways by which APP may be processed: the non-amyloidogenic and the amyloidogenic pathways. In the non-amyloidogenic pathway, APP is cleaved by an enzyme termed β-secretase directly in the portion of APP where Aβ sits; processing of APP by β-secretase thereby precludes production of Aβ. In the amyloidogenic pathway, APP is first cleaved by β-secretase at the amino (NH_2) border of Aβ and then by β-secretase, an enzyme complex that includes presenilin as one of its main components. Mutations in the genes associated with AD (APP, PS1, and PS2) each lead to increased processing of APP via the amyloidogenic pathway. The discovery of these genes (and their effects on Aβ production) is arguably the main impetus behind the Amyloid Cascade Hypothesis (Arbor et al, 2016; MacLeod et al, 2015).

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Amyloid Beta Isoforms

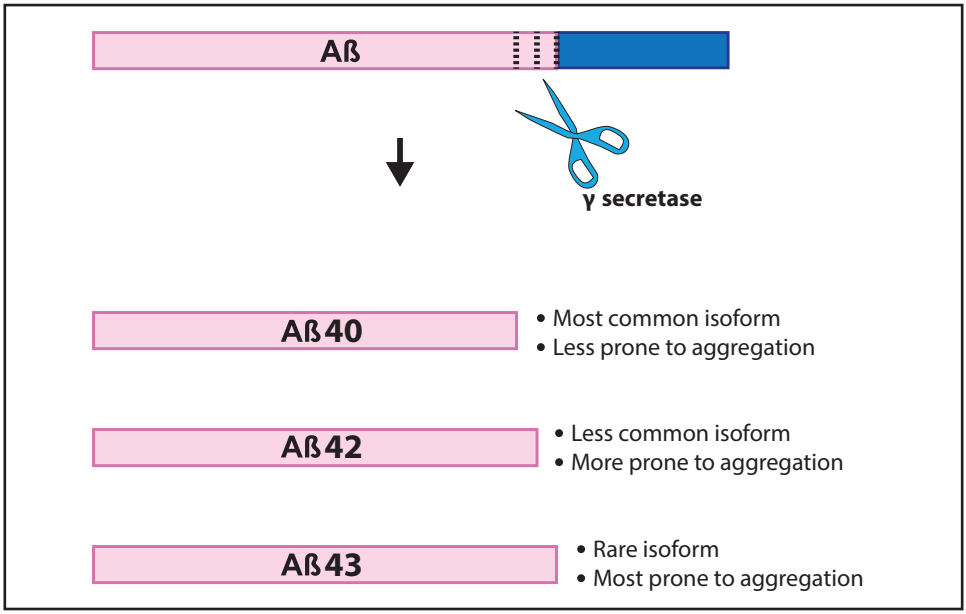

FIGURE 1.5. Gamma-secretase cleavage yields Aβ proteins ranging from 39 to 43 amino acids long. The Aβ40 isoform is the most common form; however, the Aβ42 isoform is more prone to aggregation into oligomers and is considered the more toxic form of Aβ. The Aβ43 isoform is relatively rare but is thought to be even more prone to aggregation than the Aβ42 isoform (Arbor et al, 2016; MacLeod et al, 2015).

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Alzheimer's Disease Pathology: Amyloid Beta

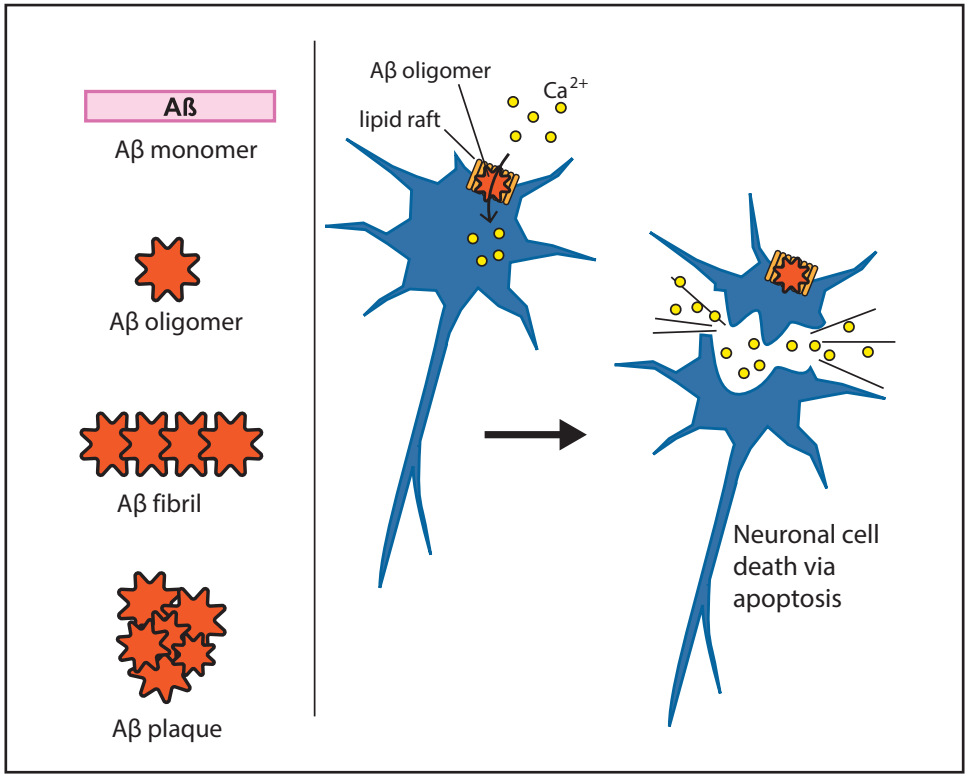

FIGURE 1.6. Although the accumulation of Aβ into plaques is a hallmark feature of AD, the most recent data indicate that it is the oligomeric form of Aβ (made from an accumulation of monomeric Aβ) and Aβ fibrils (formed by strings of Aβ oligomers) that may be the most toxic to the brain. One way in which Aβ oligomers may be toxic to neurons is via their effects on Ca^{2+} homeostasis within neurons. Aβ has been shown to form Ca^{2+} channels within the neuronal cell membrane, particularly in lipid raft domains. The resultant increase in Ca^{2+} influx via Aβ channels may ultimately lead to neuronal cell death via apoptosis (Arbor et al, 2016; MacLeod et al, 2015).

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Is Amyloid Beta a Good Thing?

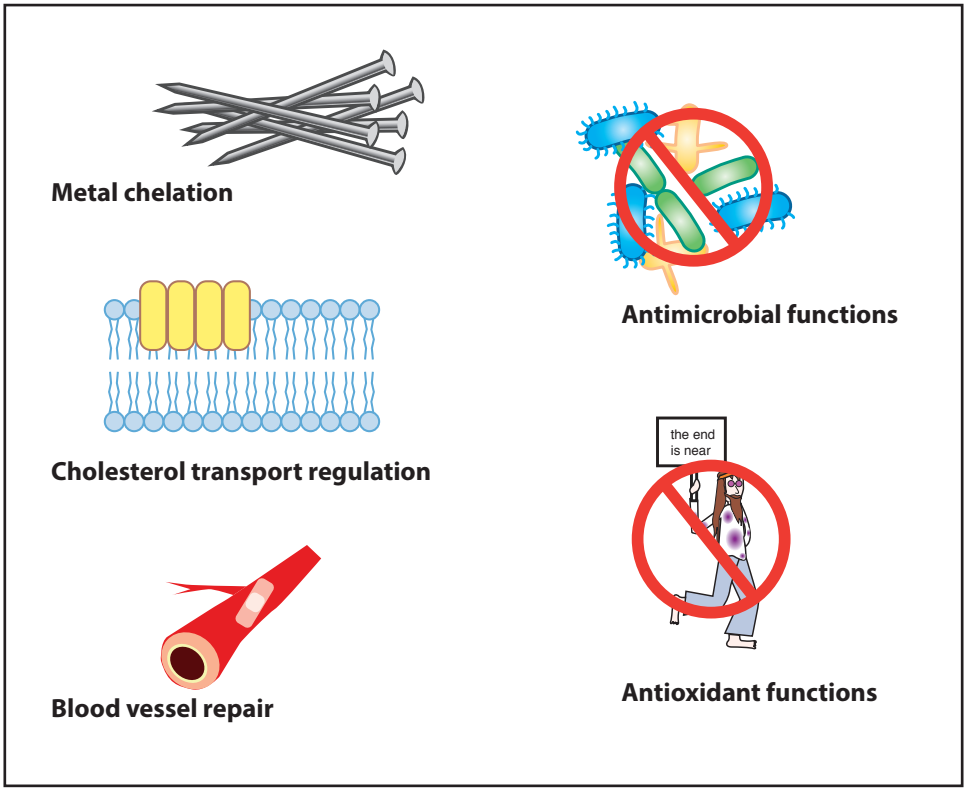

FIGURE 1.7. Although the production of Aβ has been historically associated with negative, pathological processes, it is a normal, healthy molecular process that we are only beginning to understand. Amyloid beta production has been hypothesized to have several potentially beneficial properties including chelation of metal ions; regulation of cholesterol transport; vessel repair; antimicrobial functions; and antioxidant activities, all of which may lend Aβ the ability to protect the brain as it ages, but may become pathologic under trying circumstances (Anand et al. 2012; Atwood et al, 2002; Atwood et al, 2002b; Kokjohn et al, 2012; Kumar et al, 2016; Cárdenas-Aguayo et al, 2014).

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Alzheimer's Disease Pathology: Tangles

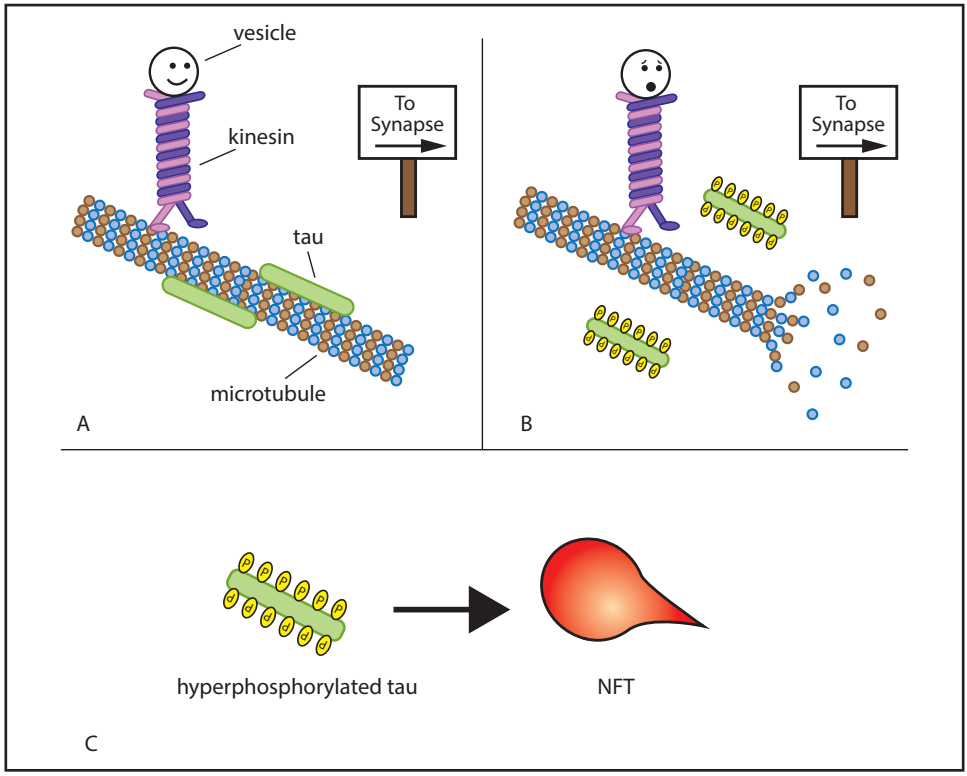

FIGURE 1.8. (A) Tau is a microtubule-associated binding protein and, in its non-pathological form, it binds to and stabilizes microtubules within axonal projections. It is along these microtubules that synaptic vesicles carrying neurotransmitters are transported to the synapse. (B) When hyperphosphorylated tau (pTau) is no longer able to bind microtubules, destabilization of microtubules and synaptic dysfunction results. (C) Hyperphosphorylated tau also forms paired helical filaments which then aggregate into the neurofibrillary tangles (NFTs) observable in the postmortem AD brain (Arendt et al, 2016).

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Tauopathies

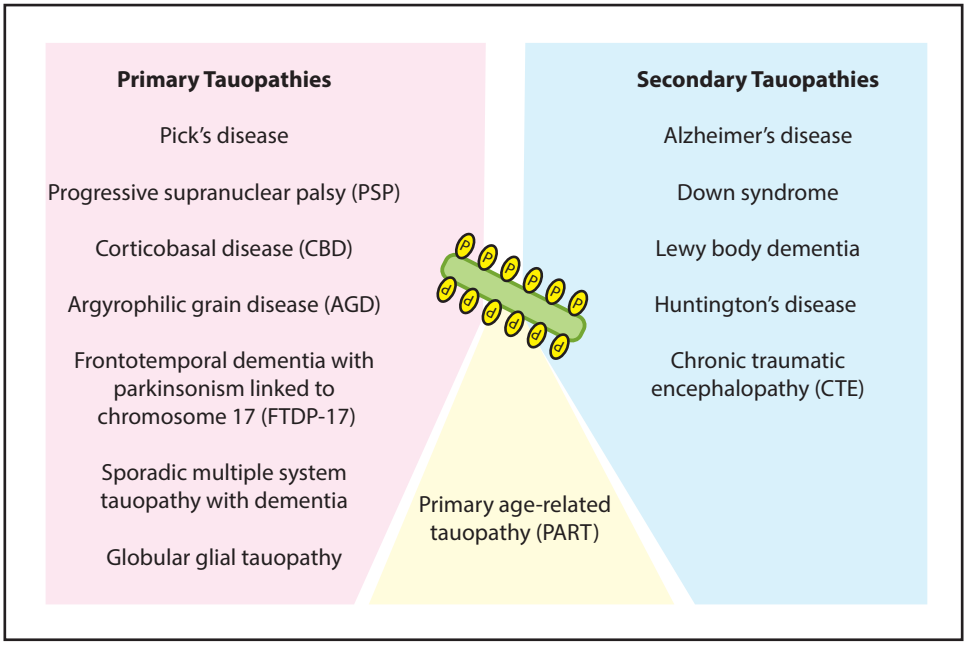

FIGURE 1.9. Alzheimer's disease is only one type of dementia in which there is a pathological build-up of tau protein (i.e., AD is only one type of tauopathy). There are other tauopathies, some considered "primary" (tau is thought to be the driving pathological entity) and others, such as AD, considered "secondary" (a pathological entity other than tau is considered to be the driving force) (Arendt et al, 2016). Interestingly, there are some elderly individuals who exhibit only tau pathology (termed primary age-related tauopathy or PART); such individuals typically do not exhibit severe cognitive deficits or dementia. Thus, one might suppose that it is not tau (nor Aβ) accumulation that brings about dementia, but a cumulative process in which Aβ and tau may be the resultant features (Dugger and Dickson, 2017; Maloney and Lahiri, 2016).

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Alzheimer's Disease Pathology: Neuronal Death

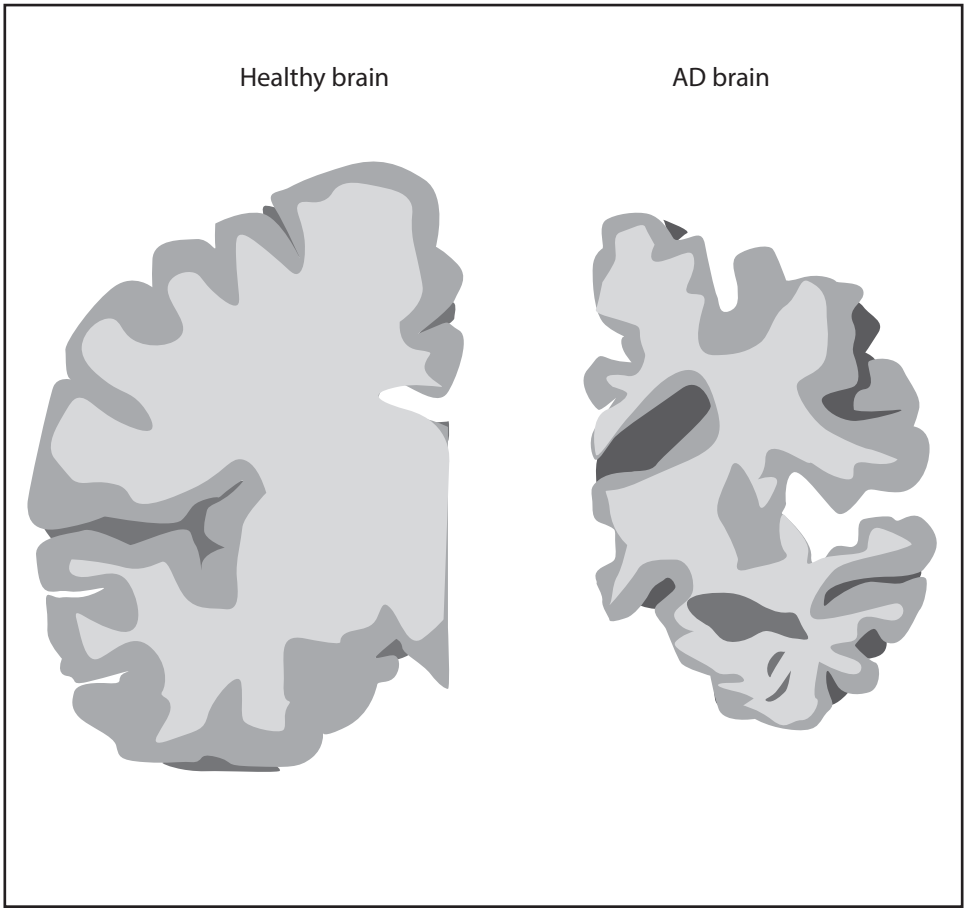

FIGURE 1.10. The loss of neurons is often so profound that it can be seen upon postmortem gross examination of the brain. Loss of neurons occurs in limbic and cortical regions and profoundly affects cholinergic neurons, although other neurotransmitter systems are also impacted. Neuronal cell death in AD is hypothesized to arise from several different factors including toxic oligomeric forms of Aβ, accumulated tau proteins, oxidative stress, and excitotoxicity (Pepeu and Giovannini, 2017; Alzheimer's Association, 2017).

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Inflammation in Alzheimer's Disease

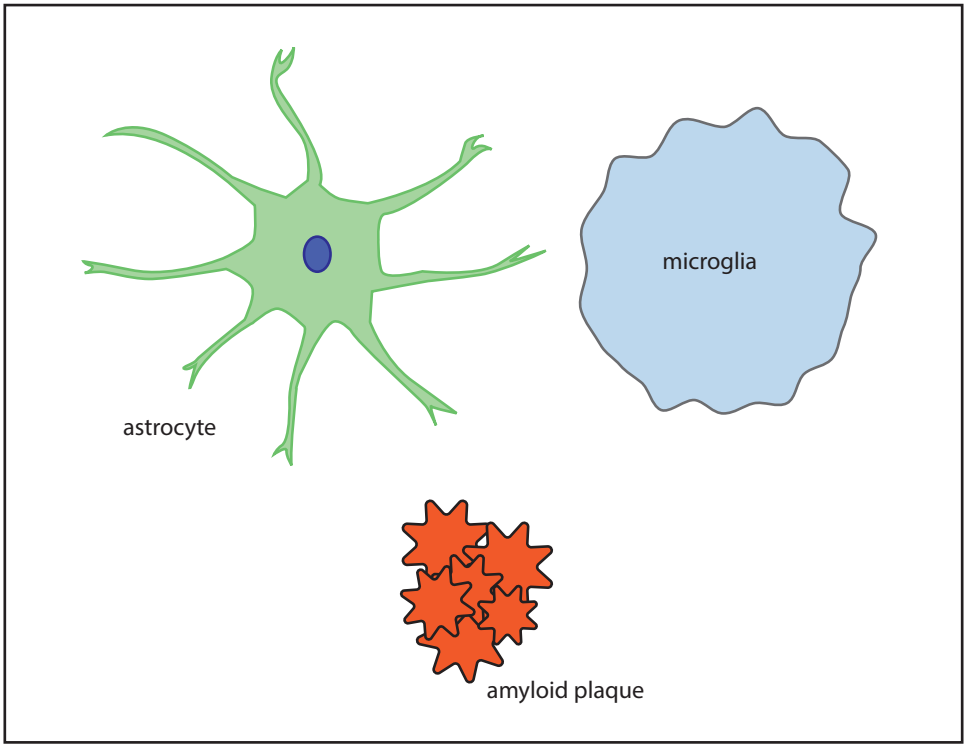

FIGURE 1.11. In the AD brain, Aβ plaques and NFTs are often surrounded by activated microglia and astrocytes, the brain's primary defense cells, indicating a substantial immune reaction in the AD brain. Many researchers hypothesize that Aβ (and possibly tau) set off an immune response in the brain that is intended to protect neurons from pathological entities. However, as the accumulation of pathological Aβ and tau levels increase, the brain's immune system becomes overwhelmed and inflammatory processes (including the release of cytokines and other inflammatory molecules) lead to the initial immune reaction, causing more harm than benefit to the brain. Proinflammatory factors may also increase amyloidogenic processing of APP, bringing about increased production of Aβ42 as well as hyperphosphorylation of tau (Bronzuoli et al, 2016; Ransohoff, 2016; Schwartz and Deczkowska, 2016).

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The Amyloid Cascade Hypothesis

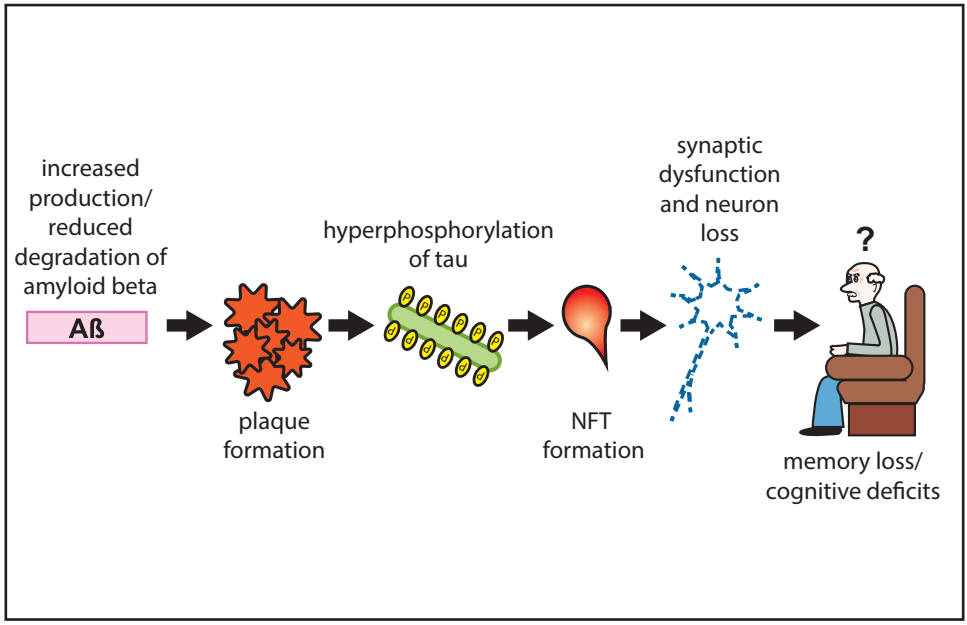

FIGURE 1.12. The leading hypothesis regarding the neurobiological progression of AD—the Amyloid Cascade Hypothesis—posits that the Aβ protein begins to accumulate in the brain with age due either to increased production or decreased degradation of Aβ and as a result of genetic and/or environmental factors. As Aβ accumulates, it also causes activation of several kinases (including glycogen synthase kinase 3β [GSK-3β], cAMP-dependent protein kinase [PKA], and cyclin-dependent protein kinase 5 [CDK-5]); these kinases cause hyperphosphorylation of tau. As AD progresses, synaptic dysfunction spreads, neurons are destroyed, and clinical signs of AD become increasingly severe (Mendiola-Precoma et al, 2016; Stahl, 2013).

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Is The Amyloid Cascade Hypothesis Correct?

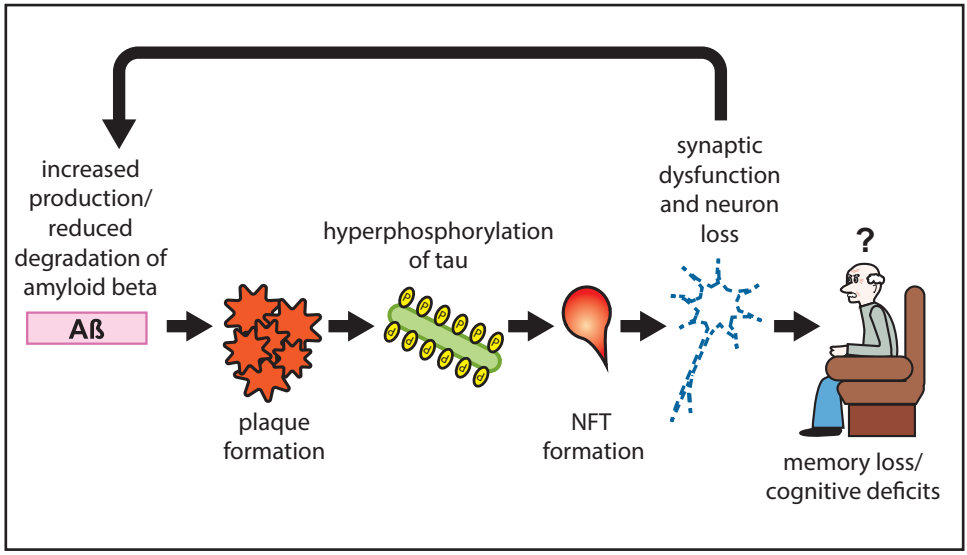

FIGURE 1.13. Not all experts are convinced that the Amyloid Cascade Hypothesis is correct, especially given the failure of all clinical trials utilizing treatments that target Aβ in patients with AD. However, proponents of the Amyloid Cascade Hypothesis claim that previous anti-amyloid clinical trials have failed not because the Amyloid Cascade Hypothesis is wrong, but because the subjects enrolled in such trials have been too far progressed in terms of the irreversible damage to the brain. All previously failed trials have enrolled patients with, at worst, clinically diagnosable AD or, at best, mild cognitive impairment (MCI), the clinical precursor to AD. Many Amyloid Cascade Hypothesis supporters theorize that once the amyloid cascade is set into motion, the detrimental effects (including oxidative stress, inflammation, the formation of neurofibrillary tangles [NFTs], and synaptic dysfunction) become a self-perpetuating cycle of destruction whereby Aβ accumulation becomes irrelevant. Accordingly, it is thought that anti-amyloid therapies must be initiated at the earliest sign of Aβ accumulation possible—before the amyloid cascade is irreversibly set into motion (and consequently before clinical signs of AD or even MCI are evident) (Alzheimer's Association, 2017; Arendt et al, 2016; Harrison and Owen, 2016).

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Interaction of Aβ and Tau

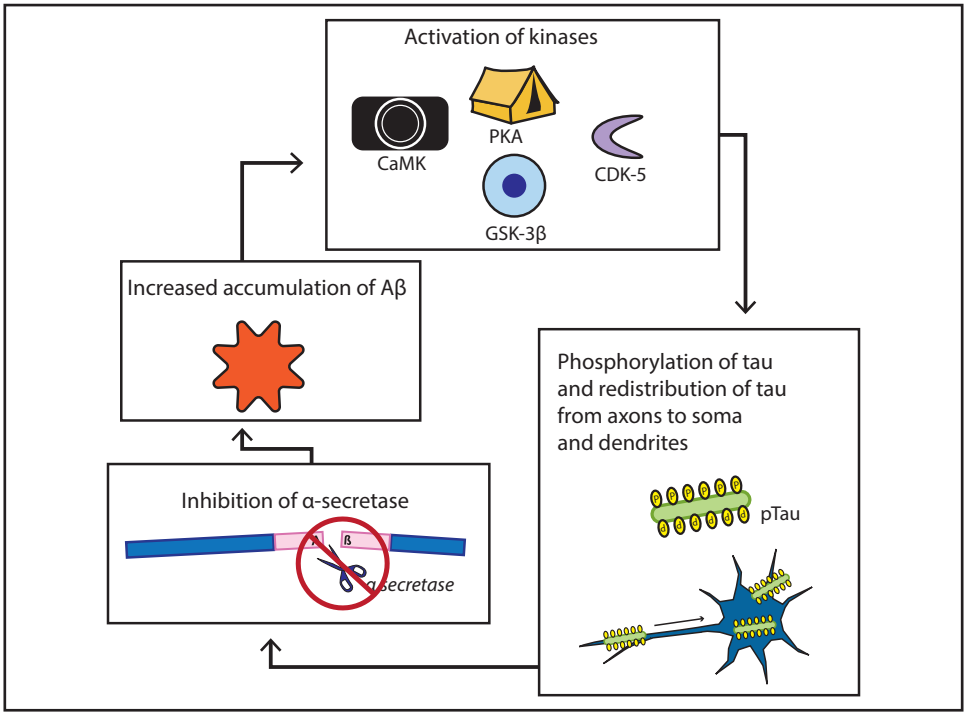

FIGURE 1.14. Most data support the hypothesis that Aβ sparks the hyperphosphorylation of tau in the AD brain. Not only may Aβ activate kinases such as glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase-5 (CDK-5), cAMP-dependent protein kinase (PKA), and Ca^{2+}/calmodulin-dependent protein kinase-II (CaMKII) that phosphorylate tau, oligomeric Aβ, in particular, may also cause the redistribution of tau from axons to neuronal soma and dendrites, further disrupting neuronal function. There is also evidence that hyperphosphorylated tau (pTau) may actively drive Aβ pathology as well. One proposed mechanism for this is the pTau-induced inhibition of non-amyloidogenic (i.e., β-secretase) processing of amyloid precursor protein (APP). Thus, once the cascade of events initiated by Aβ has begun, a self-perpetuating cycle of pathological feedback is maintained (Arendt et al, 2016).

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Familial Alzheimer's Disease

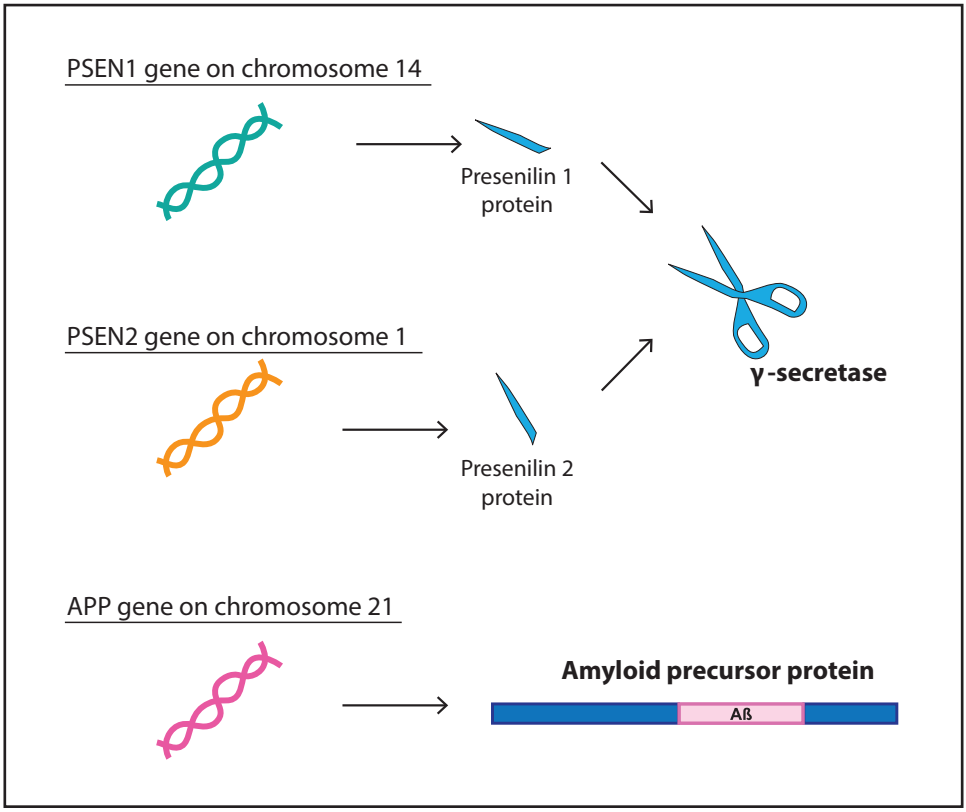

FIGURE 1.15. A small portion (~1%) of AD cases are familial—caused by mutations in one of three genes (presenilin 1 [PSEN1], presenilin 2 [PSEN2], or amyloid precursor protein [APP]). Amyloid beta (Aβ), a pathological protein that accumulates in AD, is cleaved from APP by β-secretase, an enzyme complex that contains presenilins. Inheritance of a mutation in any one of these genes leads to an increase in the production or pathogenicity of Aβ and the inevitable development of clinically diagnosable AD, typically before the age of 65 (Giri et al, 2016; Hinz and Geschwind, 2017).

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Amyloid Precursor Protein Mutations

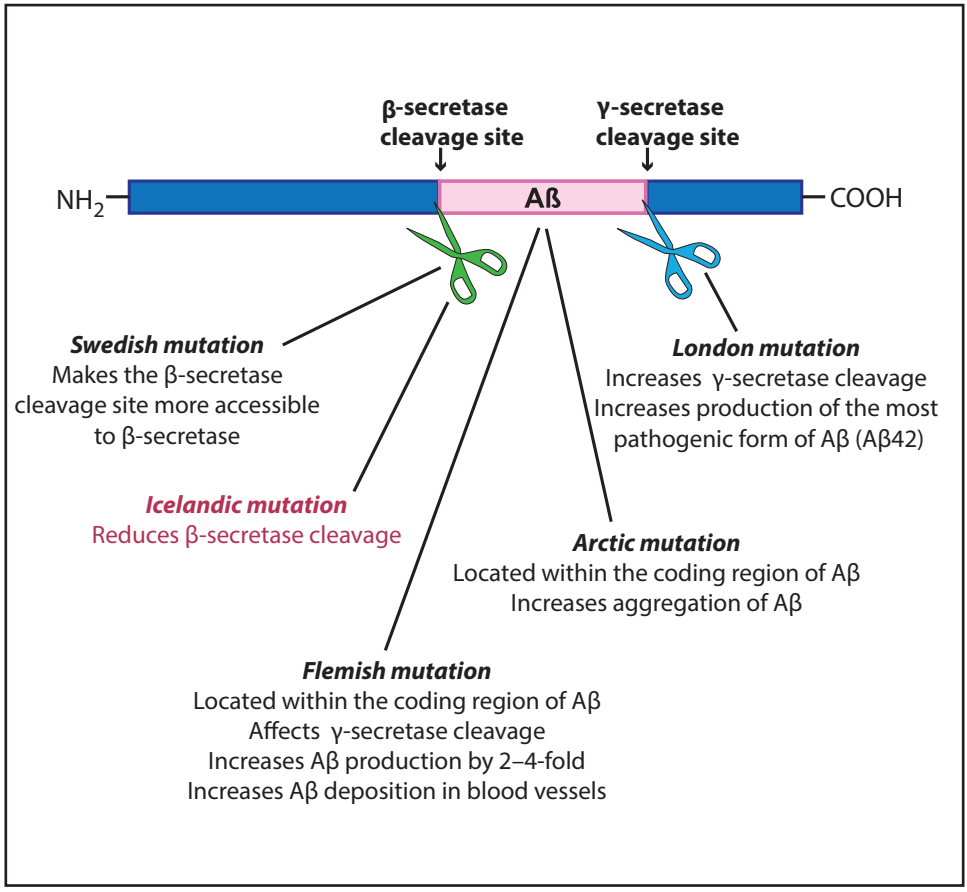

FIGURE 1.16. There are nearly 300 different AD-related mutations that have so far been discovered in the APP gene (including the Swedish, Arctic, London, and Flemish mutations) that are associated with familial AD. Most of these mutations can be found within or near the sites where Aβ is cleaved from APP (i.e., beta- and gamma-secretase cleavage sites). Another mutation, the Icelandic, has recently been discovered; individuals with the Icelandic mutation in APP appear to be protected from the development of AD (Giri et al, 2016; Hinz and Geschwind, 2017; Rosenberg et al, 2016; Schellenberg and Montine, 2012).

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Presenilin Mutations

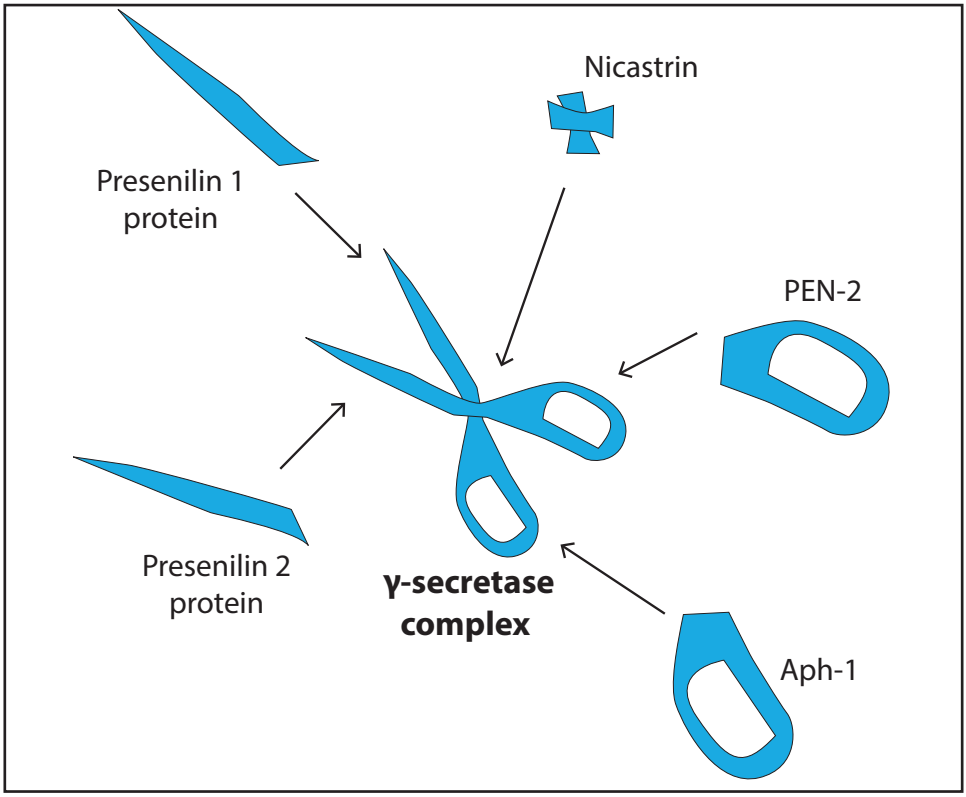

FIGURE 1.17. The PSEN1 and PSEN2 genes code for presenilins, which are active portions of the γ-secretase enzyme that cleaves APP (along with nicastrin, anterior pharynx-defective-1 [Aph-1], and presenilin-enhancer-2 [PEN-2]. There are 215 AD-related mutations in PSEN1 that have been discovered to-date, and these PSEN1 mutations account for approximately 50% of all familial, early-onset cases of AD; mutations in PSEN2 (of which 13 have so far been revealed) are far less common. Both PSEN1 and PSEN2 mutations lead to increased production of the more toxic Aβ42 protein, with the effects of PSEN1 mutations being more severe than those associated with PSEN2 mutations (Giri et al, 2016; Hinz and Geschwind, 2017).

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Down Syndrome

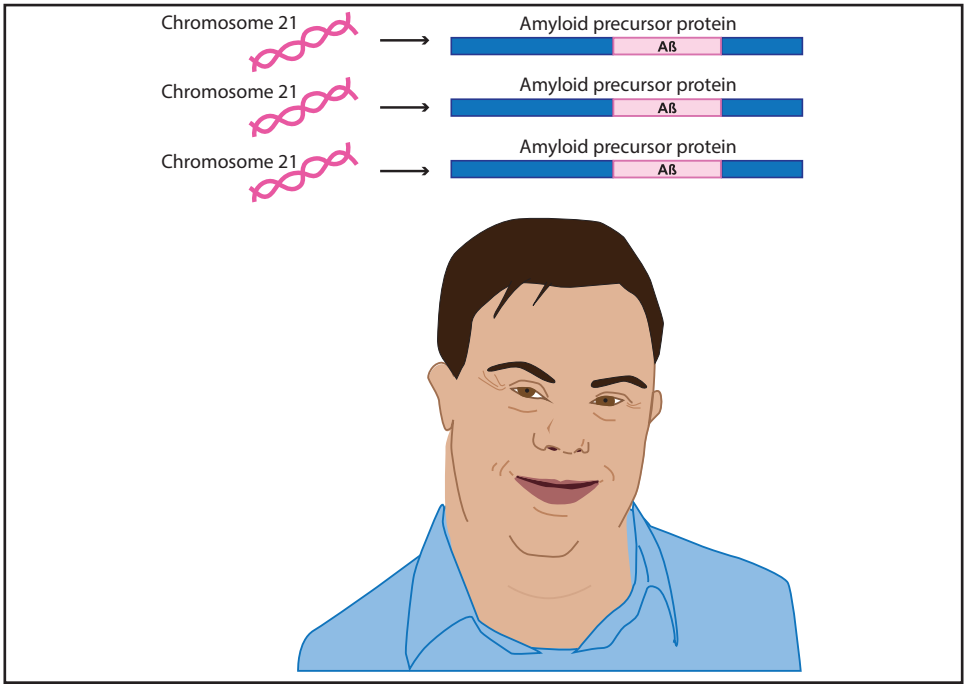

FIGURE 1.18. Individuals with Down syndrome have three copies of chromosome 21 (trisomy 21), thus they have three copies of the APP gene (individuals without trisomy 21 have only two copies). Due to the extra copy of the APP gene, individuals with Down syndrome produce excess APP protein and consequently have increased production and accumulation of Aβ. As a result, most individuals with Down syndrome have Alzheimer's pathology present in the brain by age 40, and most individuals with Down syndrome over the age of 70 exhibit Alzheimer's-type dementia (Ballard et al, 2016; Hithersay et al, 2017).

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Sporadic Alzheimer's Disease

Increased Risk	Decreased Risk
Head injury	Cognitive stimulation
African–American race	Exercise
Depression	Mediterranean diet
Cardiovascular disease	Increased education
Diabetes	Social engagement
APOEε4 allele	APP Icelandic mutation
Additional genetic factors	Additional genetic factors

FIGURE 1.19. The vast majority of AD cases are sporadic—caused not by a single genetic polymorphism but by the combination of a plethora of identified and unidentified genetic and environmental factors (including apolipoprotein 4 [APOE4] allele status, education level, and cardiometabolic factors). Likewise, there are several environmental and lifestyle factors that appear to convey some protection against the development of AD, such as social engagement and exercise (Alzheimer's Association, 2017; Jonsson et al, 2012; Hardman et al, 2016; Larson et al, 2006; Lee et al, 2016; Michel, 2016; Uzun et al, 2011; Yaffe et al, 2012).

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Alzheimer's Disease Risk Genes

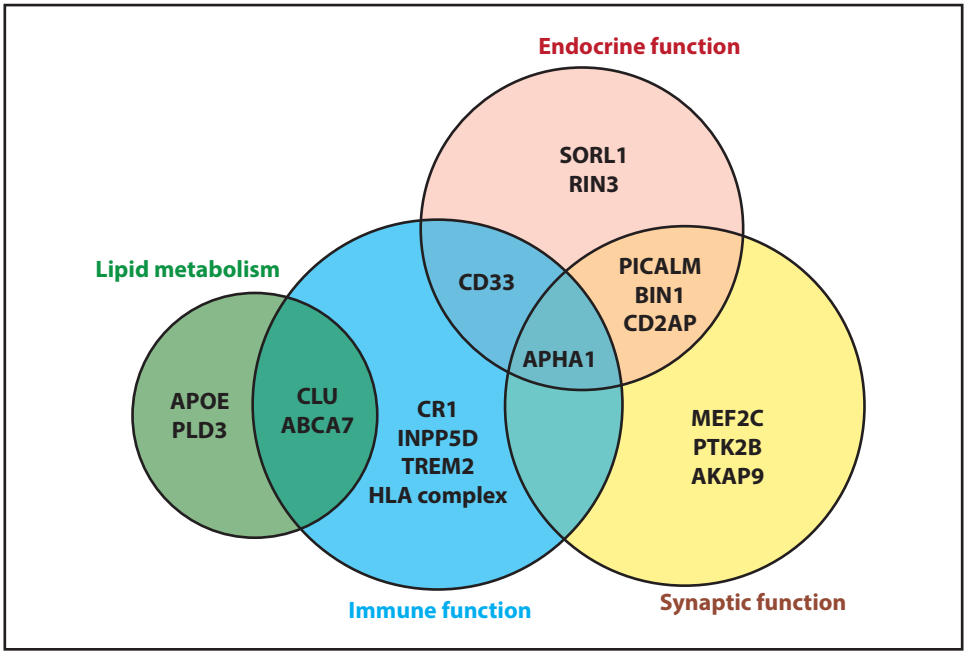

FIGURE 1.20. Numerous genetic polymorphisms have been indicated as increasing one's risk of developing AD. These genes largely fall into four categories in terms of their function: immunity, synaptic function, endocytosis, and lipid metabolism. Although inheritance of any one of these polymorphisms will not invariably lead to the development of AD, inheritance of several of these polymorphisms (in combination with environmental and other genetic factors) is hypothesized to accumulate into an increased risk of developing AD (Hinz and Geschwind, 2017).

ABCA7: ATP binding cassette subfamily A member 7; AKAP9: A-kinase anchoring protein 9; APHA1: aminoglycoside phosphotransferase A1; APOE: apolipoprotein E; BIN1: bridging integrator 1; CD2AP: cluster of differentiation 2-associated protein; CD33: cluster of differentiation 33; CLU: clusterin; MEF2C: myocyte enhancer factor 2C; PICALM: phosphatidylinositol-binding clathrin assembly protein; PLD3: phospholipase D family member 3; PTK2β: protein tyrosine kinase 2 beta; RIN3: renin angiotensin system (Ras) and Ras-associated binding protein (Rab) interactor 3; SORL1: sortilin-related receptor 1

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Apolipoprotein E

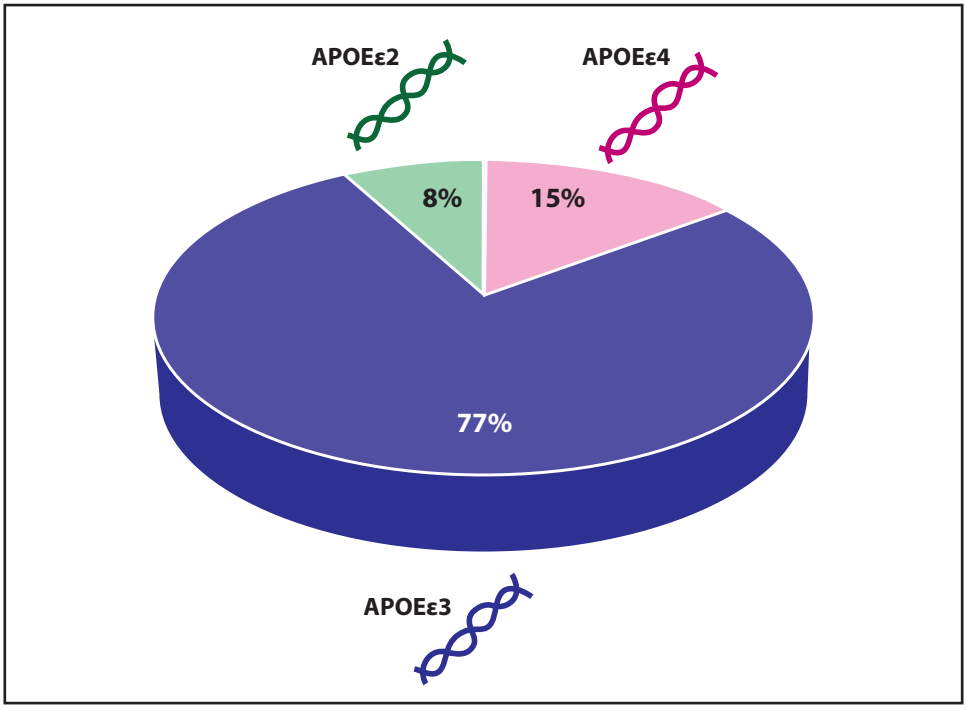

FIGURE 1.21. Of the genetic factors that contribute to the risk of developing AD, the gene for apolipoprotein E (APOE) appears to have the greatest influence. APOE is a protein that transports the cholesterol needed by neurons for synapse development, dendrite formation, long-term potentiation, and axonal guidance. APOE is also hypothesized to have an intricate relationship with amyloid beta (Aβ) whereby it may affect Aβ metabolism, aggregation, and deposition in the brain. Inheritance of even one copy of the APOEϒ4 allele increases the risk of developing AD by 3×; inheritance of two copies of APOEϒ4 increases the AD risk by 10×. Conversely, the APOEϒ2 allele appears to offer some protection from AD whereas the APOEϒ3 allele (the most common form of the APOE gene) conveys a risk that falls between APOEϒ2 and APOEϒ4. Approximately 15% of individuals in the general population carry the APOEϒ4 allele; however, among individuals with AD, 44% carry the APOEϒ4 allele (Alzheimer's Association, 2017; Arbor et al, 2016; Deypere et al, 2016; Giri et al, 2016; Hinz and Geschwind, 2017; Maloney and Lahiri, 2016).

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Cholesterol and Alzheimer's Disease

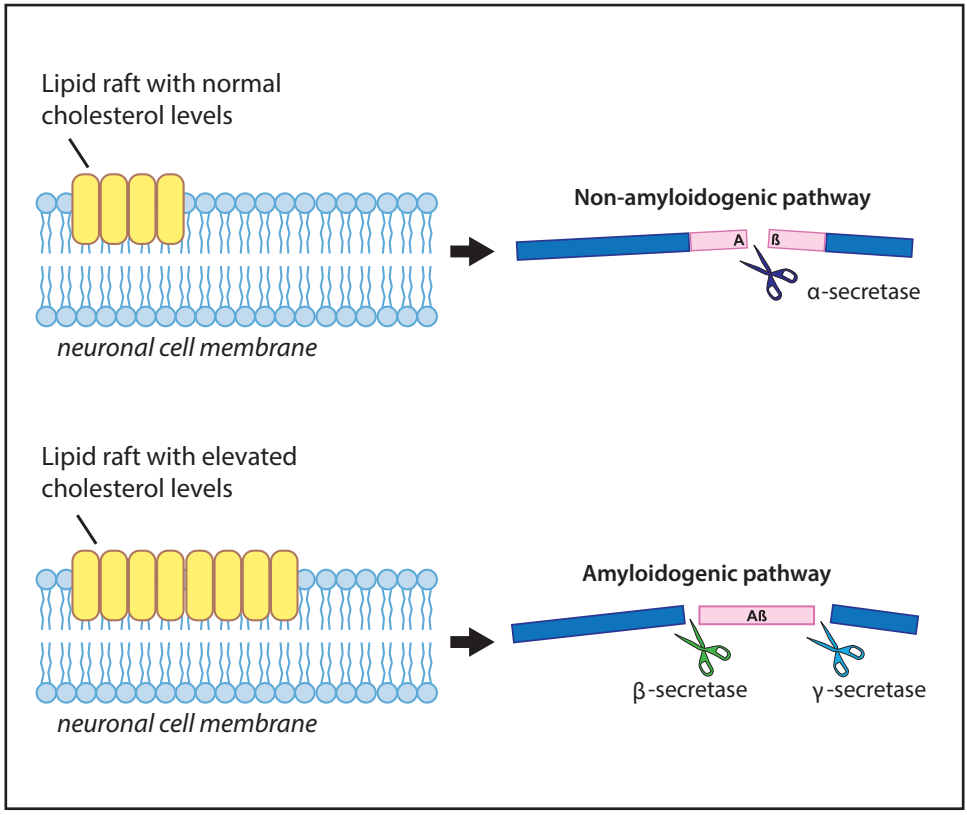

FIGURE 1.22. The brain contains 20% of the body's cholesterol, primarily in myelin sheaths and also, importantly, in lipid rafts. Lipid rafts are areas of the cell membrane that are critical for protein movement into and out of neurons, signal transduction, and neurotransmission. Of interest, Ɣ-secretase cleavage of APP occurs within lipid rafts and, as aforementioned, Aβ oligomers are capable of forming Ca^{2+} channels within lipid rafts. Alterations in brain cholesterol levels have been shown to modify APP metabolism whereby ideal brain cholesterol levels may promote non-amyloidogenic (Ɣ-secretase) processing of APP (and lower Aβ production) whereas elevated brain cholesterol levels may increase amyloidogenic (β- and Ɣ-secretase) processing of APP (and consequently increase Aβ production) (Arbor et al, 2016; Mendiola-Precoma et al, 2016).

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Type 3 Diabetes?

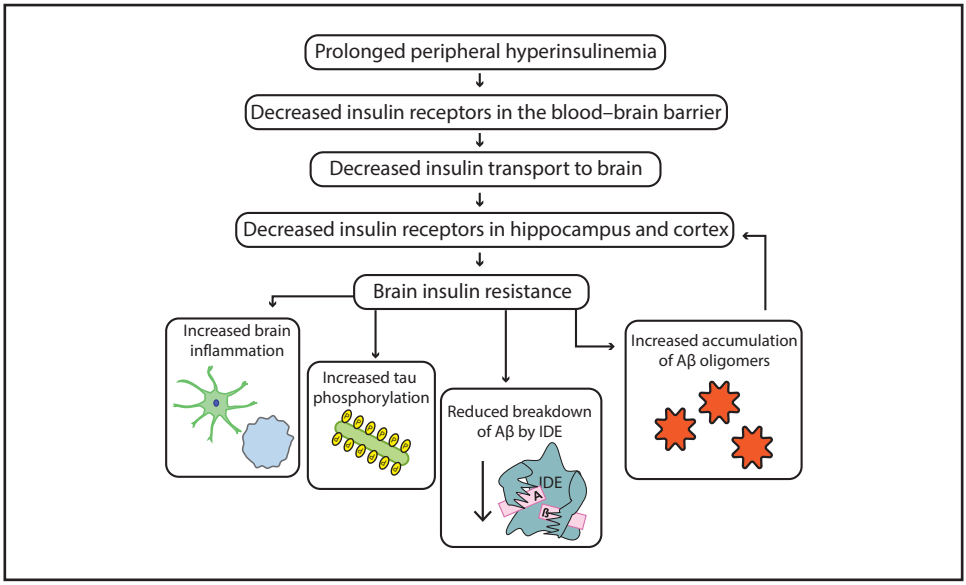

FIGURE 1.23. Individuals with Type 2 diabetes have a 2× greater risk of developing AD. In fact, it has been proposed that AD might represent a "Type 3" diabetes. Patients with AD not only show decreased insulin sensitivity in the periphery and a higher rate of Type 2 diabetes but also have increased insulin resistance and decreased insulin receptor expression within the brain, as well as decreased insulin transport into the brain. These insulin abnormalities are most notable in the medial temporal lobe—an area greatly affected in AD—and may be exacerbated by Aβ accumulation. Additionally, insulin degrading enzyme (IDE) not only breaks down insulin but also Aβ; with decreased insulin levels in the brain, there is a concomitant decrease in IDE levels. Given the association of Type 2 diabetes with obesity, the AD-as-Type-3-diabetes hypothesis may be one way in which certain lifestyle factors (e.g., high fat diet, low exercise) may increase one's risk of developing AD. In addition to modification of lifestyle factors that are beneficial in managing or preventing AD, intranasal delivery of insulin (providing a direct route to the brain) shows some promise in improving cognition and potentially decreasing AD risk (Chakraborty et al, 2017; Kullmann et al, 2016; Lee et al, 2016; Zillox et al, 2016).

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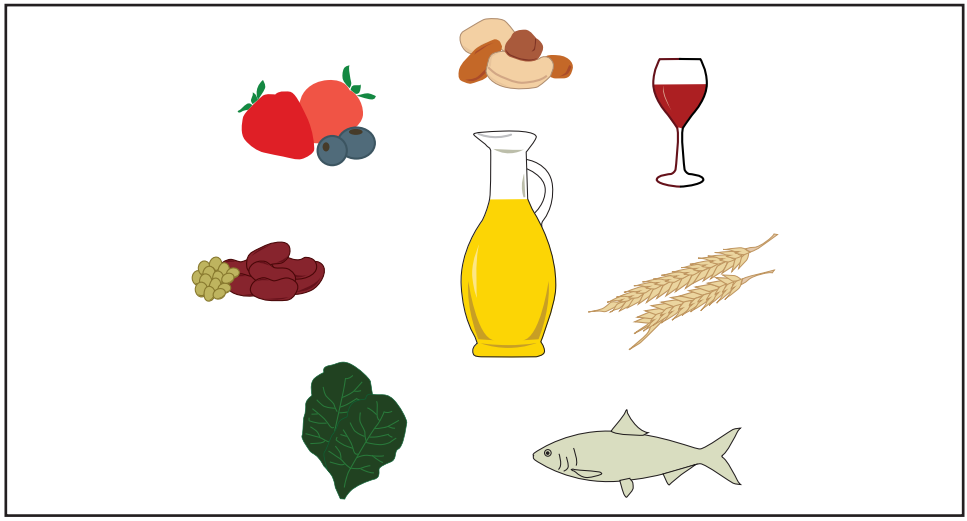

FIGURE 1.24. Numerous nutritional factors have been found to potentially lower one's risk, or slow the onset, of cognitive decline and dementia. Among these are long-chain omega-3 fatty acids (including monounsaturated fatty acids [MUFAs] found in olive oil and polyunsaturated fatty acids [PUFAs] such as eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] from fish); vitamins C, E, and B12; folate; flavonoids; phenols; and carotenes. One particular diet found to contain such nutrients is the Mediterranean diet (MeDi); the MeDi includes green, leafy vegetables; nuts; berries; legumes; whole grains; abundant consumption of extra virgin olive oil; regular consumption of fish; and a modest (but consistent) intake of wine; red meat and dairy products are consumed only in very limited quantities. Conversely, diets that are high in saturated fats and refined carbohydrates may add to one's risk of developing AD. Not only has the Mediterranean diet been shown to improve cardiovascular health and reduce the risk for cancer; to-date, several preclinical and epidemiological studies have shown that adherence to the Mediterranean diet may also reduce age-related brain atrophy, improve cognition (including memory), slow cognitive decline, and possibly reduce one's risk of developing dementia (Anastasiou et al, 2017; Aridi et al, 2017; Cederholm, 2017; Gu et al, 2015; Hardman et al, 2016; Knight et al, 2016; Marcason, 2015; Lim et al, 2016; Petersson and Philippou, 2016; O'Donnell et al, 2015).

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The Mediterranean Diet: Extra-Virgin Olive Oil

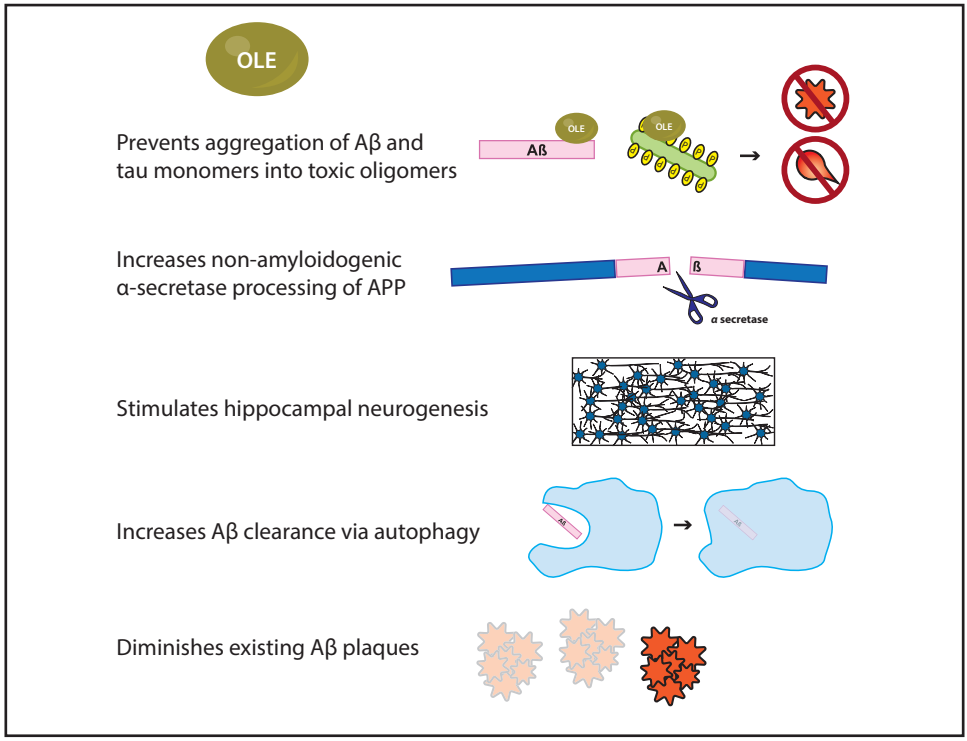

FIGURE 1.25. Accumulating data suggest that phenolic compounds (including oleuropein aglycone [OLE] and oleocanthal [OLC]), which are most notably found in extra-virgin olive oil (a staple of the Mediterranean diet), can actually thwart the pathological processes involved in Alzheimer's disease progression. Emerging data show that OLE prevents aggregation of both Aβ and tau, stimulates non-amyloidogenic processing of APP, enhances hippocampal neurogenesis, and increases clearance of Aβ (Rigacci, 2015; Qosa et al, 2015).

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The Mediterranean Diet: Extra-Virgin Olive Oil

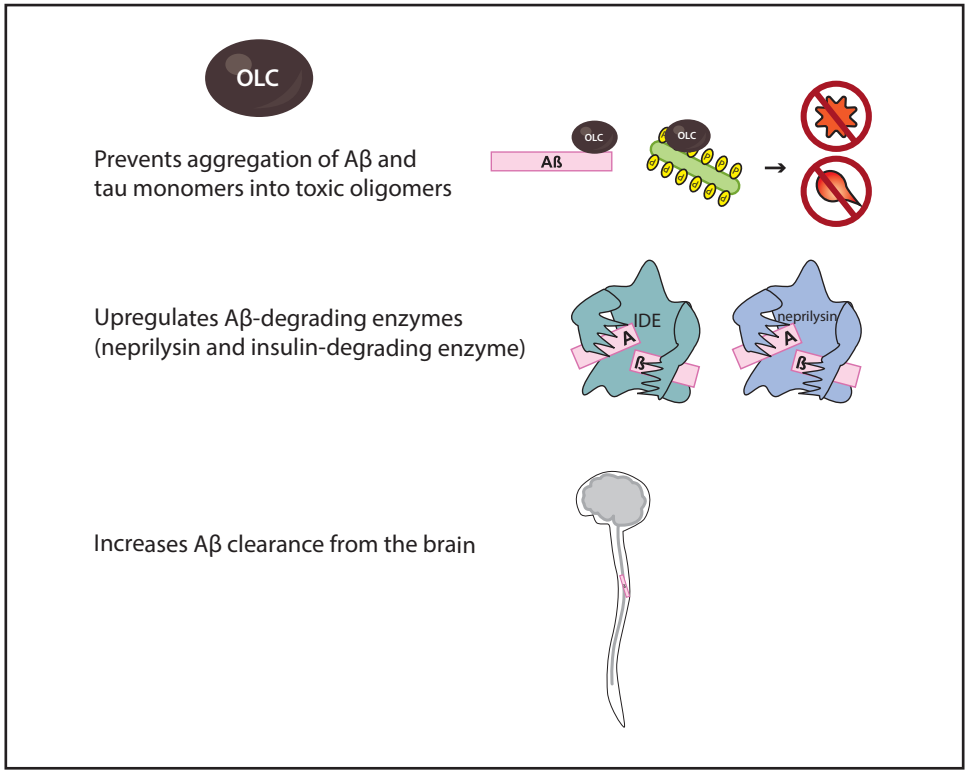

FIGURE 1.26. Similar to OLE, oleocanthal (OLC), another phenolic compound found in extra-virgin olive oil, has been shown to prevent aggregation of both Aβ and tau, as well as increasing breakdown and clearance of Aβ (Rigacci, 2015; Qosa et al, 2015).

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The FINGER Trial

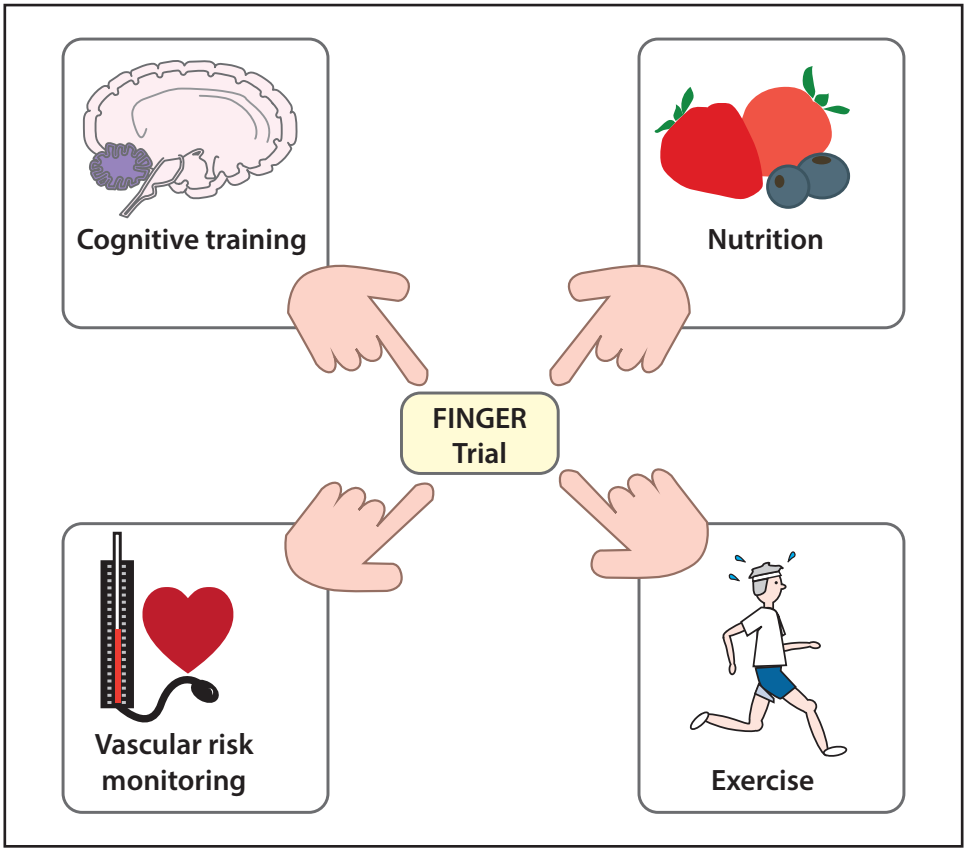

FIGURE 1.27. Recent efforts by researchers striving to test whether a multi-domain approach, involving small adjustments in several modifiable risk factors during pre-dementia phases in at-risk individuals, may halt or slow cognitive decline, and potentially dementia, are currently underway. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) and US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US POINTER) are two such ongoing trials with promising preliminary results (Ngandu et al, 2015).

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Hearing Loss in Alzheimer's Disease: Common Cause Hypothesis

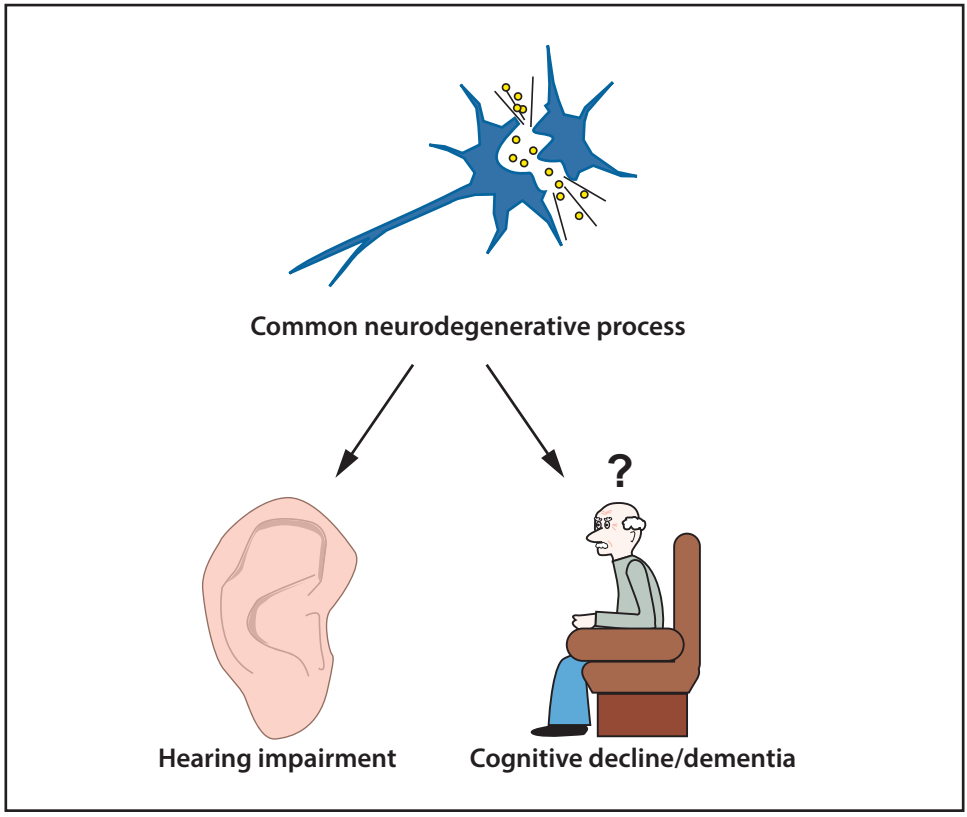

FIGURE 1.28. Hearing loss is associated with neurodegeneration and may lead to cognitive decline and increase one's risk of developing dementia. Three mechanisms by which hearing loss increases the risk of dementia have been proposed. The Common Cause Hypothesis posits that both hearing loss and cognitive decline are due to the same neurodegenerative process (Stahl, 2017).

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Hearing Loss in Alzheimer's Disease: Cascade Hypothesis

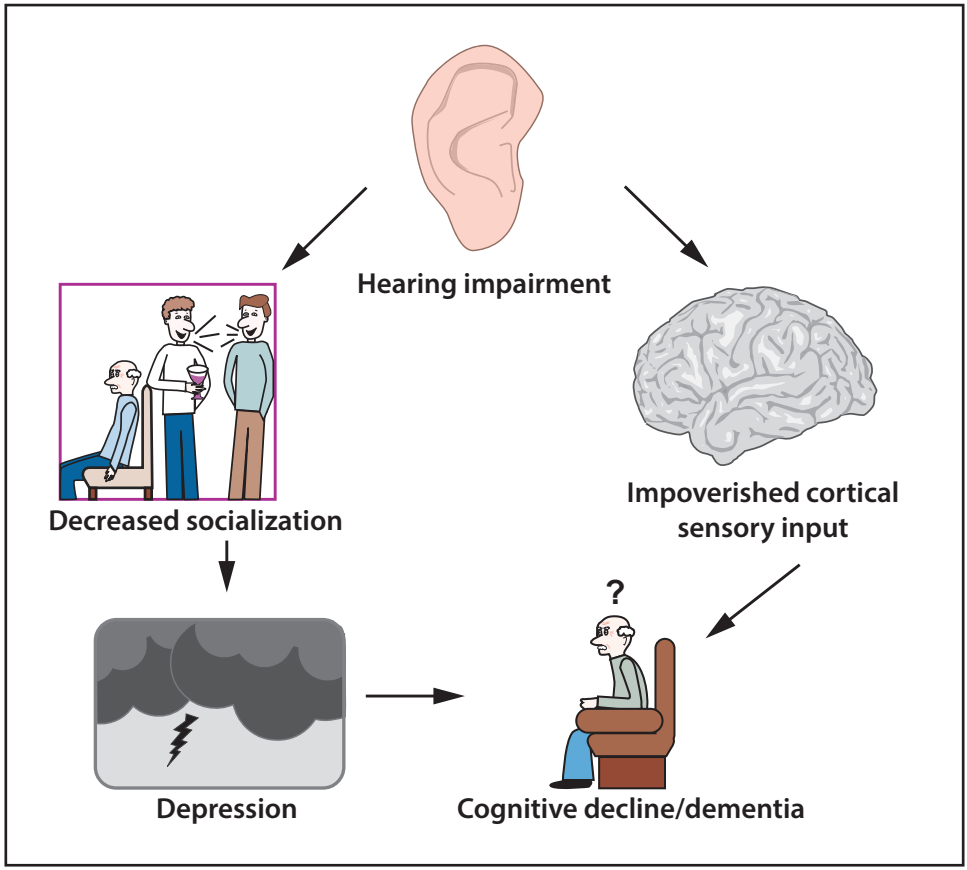

FIGURE 1.29. The Cascade Hypothesis proposes that auditory deprivation leads to cognitive decline via decreased socialization, depression, and reduced sensory input (Stahl, 2017).

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Hearing Loss in Alzheimer's Disease: Cognitive Load Hypothesis

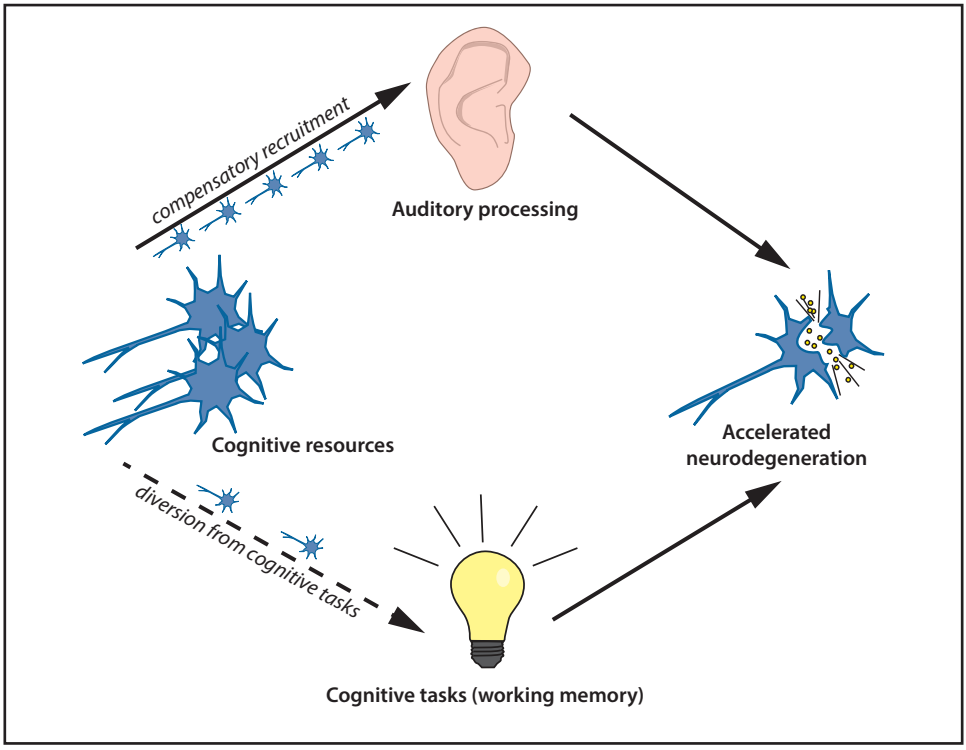

FIGURE 1.30. The Cognitive Load Hypothesis suggests that hearing loss diverts cognitive resources from memory functions to auditory processing. The three hypotheses (Common Cause, Cascade, and Cognitive Load) are not necessarily mutually exclusive; each may play a role in the connection between hearing loss and dementia. Therefore, hypothetically, treating hearing loss (e.g., with cochlear implants or hearing aids) may potentially help prevent, or delay the onset of, dementia (Stahl, 2017).

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The Importance of Early Detection

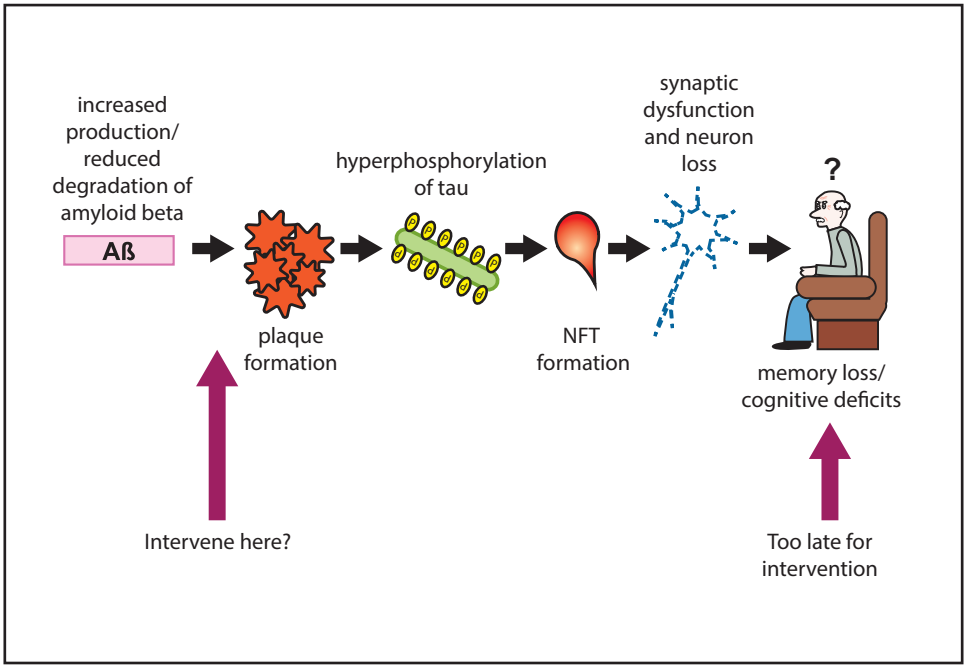

FIGURE 1.31. Until recently, patients could be diagnosed with "possible AD" based solely on clinical assessment and the confirmation of Alzheimer's disease pathology in the brain made only after death. Thus, initiating treatment before the amyloid cascade had progressed beyond the point of irreversibility was an impossibility. However, the last decade has seen tremendous advances in our ability to detect AD pathology in the living patient years before any clinical signs of cognitive impairment or dementia manifest. With these novel techniques, it is now hypothetically possible for potential AD treatments to be tested before the amyloid cascade is irreversible and before AD (or even MCI) is clinically diagnosable. In other words, if the Amyloid Cascade Hypothesis is correct, we now have the ability to possibly prevent, or at least slow, the progression of AD (Cummings, 2011; Fan and Chiu, 2010; Sharma and Singh, 2016).

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Magnetic Resonance Imaging

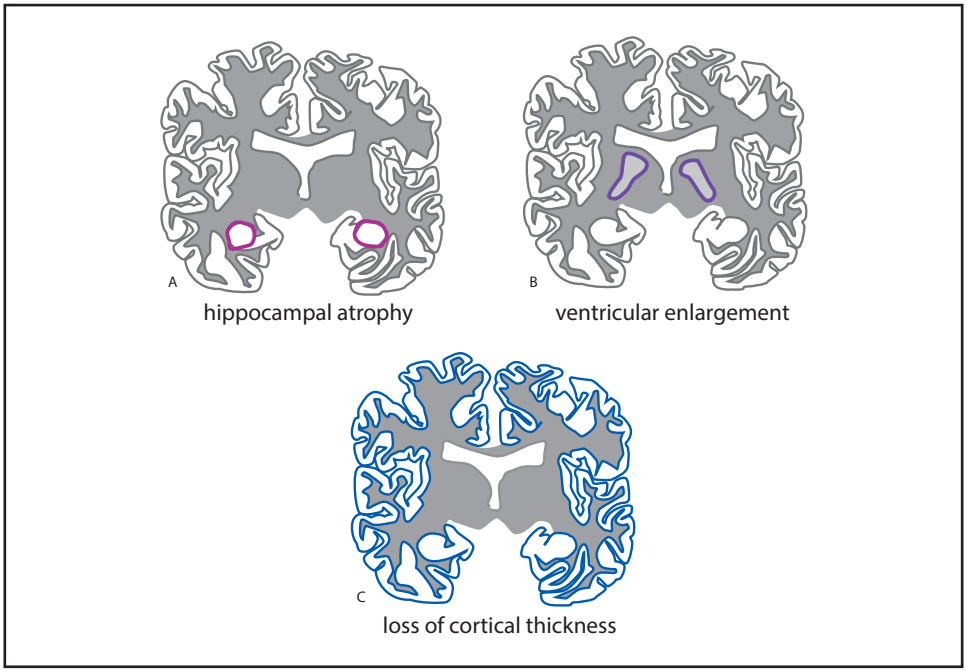

FIGURE 1.32. Magnetic resonance imaging (MRI) can detect atrophy in AD, particularly in the medial temporal lobes (including entorhinal cortex, hippocampus, amygdala, and parahippocampus). Even patients with mild AD may have 20–30% loss in entorhinal cortex volume, 15–25% loss in hippocampal volume, and ventricular enlargement. Thus, by the time a patient begins to exhibit even mild signs of dementia due to AD, damage to the brain may already be extensive and irreversible. Although the brain atrophy seen in AD usually follows a typical pattern, MRI is not diagnostic because atrophy patterns in AD can overlap with those of other diseases and some cases of AD have an atypical presentation (Johnson et al, 2011; Bonifacio and Zamboni, 2016).

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FDG-PET

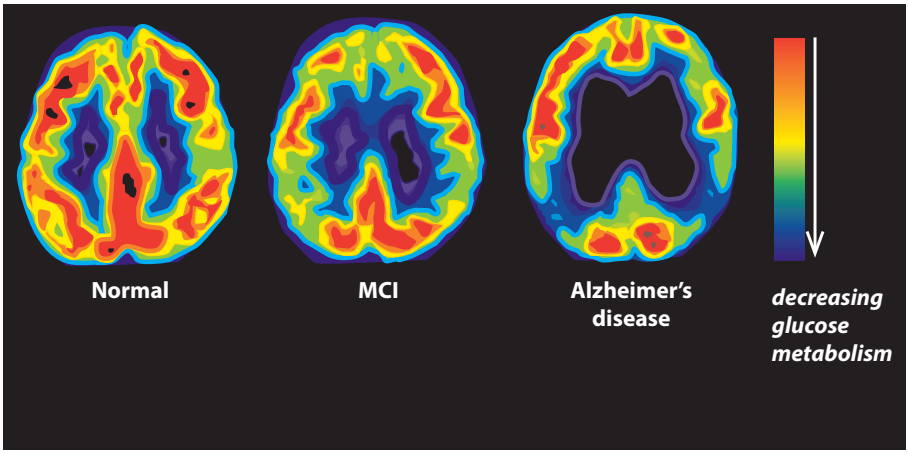

FIGURE 1.33. 18F-2-Fluoro-2-Deoxy-D-Glucose positron emission tomography (FDG-PET) measures glucose metabolism in the brain as an indirect measure of synaptic activity. The FDG-PET abnormalities seen in patients with AD may reflect a number of factors in the brain including mitochondrial dysfunction, oxidative stress, aberrant synaptic plasticity, glial activation and inflammation, reduced cerebral blood flow, and synaptic dysfunction of neuronal death (Johnson et al, 2011).

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Amyloid PET

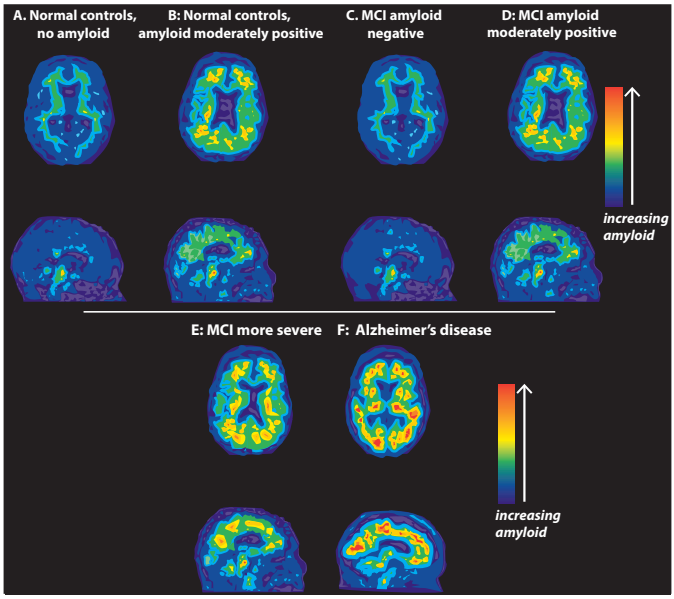

FIGURE 1.34. Several amyloid tracers have been developed; these radioligands bind to Aβ in the brain and can be visualized using positron emission tomography (PET). Although all patients with AD show Aβ pathology while using these amyloid tracers, amyloid PET cannot be used to make a definitive diagnosis of AD because as many as 40% of cognitively normal elderly individuals may have positive amyloid PET results. Cost and availability, as well as disputes regarding what threshold constitutes a "positive" amyloid PET result, have somewhat limited the use of amyloid PET in clinical practice. However, three amyloid tracers (18F-Florbetaben [Neuraceq], 18F-Florbetapir [Amyvid], and 18F-Flutemetamol [Vizamyl]) have been Food and Drug Administration (FDA)-approved to rule out (not diagnose) AD, and several other amyloid tracers are in development. While a positive amyloid PET scan does not necessarily establish a diagnosis of AD, a negative scan indicates that no Aβ pathology is present, thereby demonstrating that AD is not the cause of dementia (Anand and Sabbagh, 2017; Mallik et al, 2017; Villemagne et al, 2017).

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Tau PET

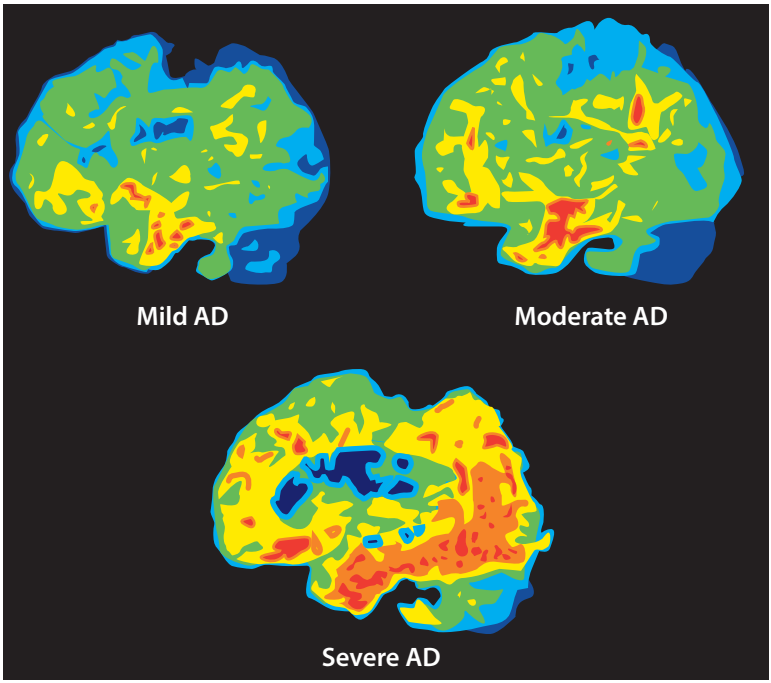

FIGURE 1.35. Radioligands that bind to tau and can be visualized using PET are also in development. Tau pathology is not unique to AD; thus like amyloid PET, a positive tau PET result is not diagnostic of AD. However, when added to the armamentarium of biomarkers for AD and other dementias, tau PET may greatly aid in the differential diagnosis of dementia (Arendt et al, 2016; Gordon et al, 2016; Villemagne et al, 2017; Kolb and Andres, 2017).

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Cerebrospinal Fluid Measures

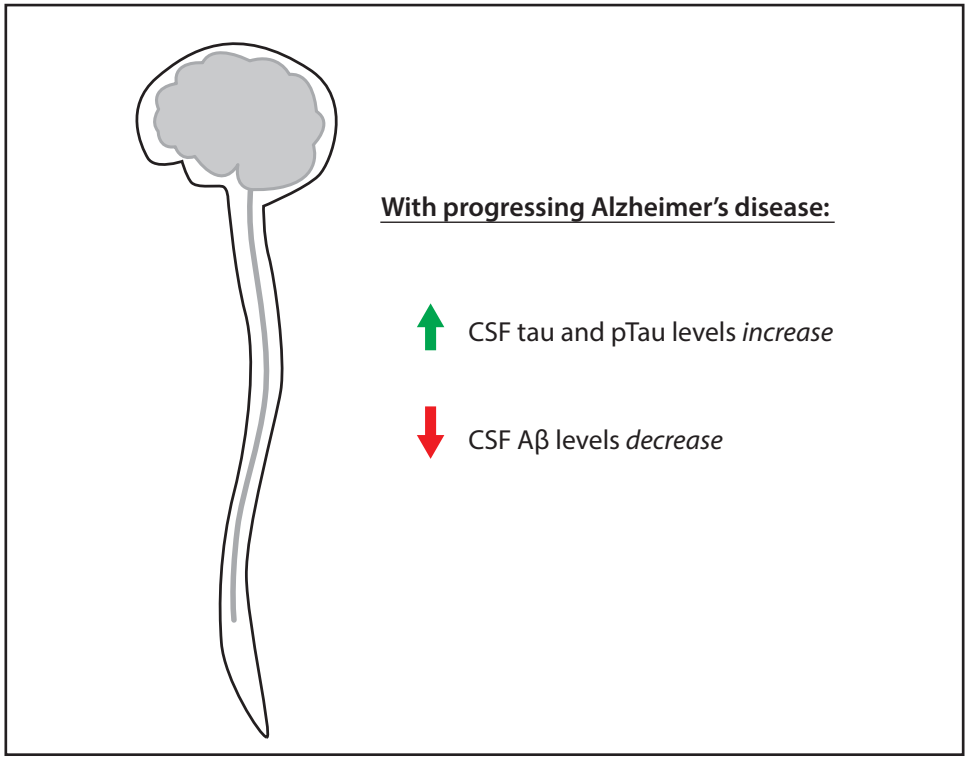

FIGURE 1.36. We now also have the ability to detect AD-related pathology using biomarkers found in the cerebrospinal fluid (CSF). As neurodegeneration in the AD brain increases, so do levels of both tau and phosphorylated tau (pTau) in the CSF. Contrary to this, measures of Aβ are actually decreased in the CSF of patients with AD. This decrease in Aβ is hypothesized to result from increased deposition of Aβ into plaques into the brain and/or decreased production of Aβ as amyloid-producing neurons in the brain die. These CSF measures can also aid in the differential diagnosis of dementia; in patients with positive CSF measures of tau but negative CSF measures of Aβ, the cause of dementia is likely a tauopathy other than Alzheimer's disease (Herukka et al, 2017; Herrmann et al, 2011; Johnson et al, 2011; Simonsen et al, 2017; Spies et al, 2013; Spies et al, 2012).

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Progression of AD Pathology, Clinical Symptoms, and Biomarkers

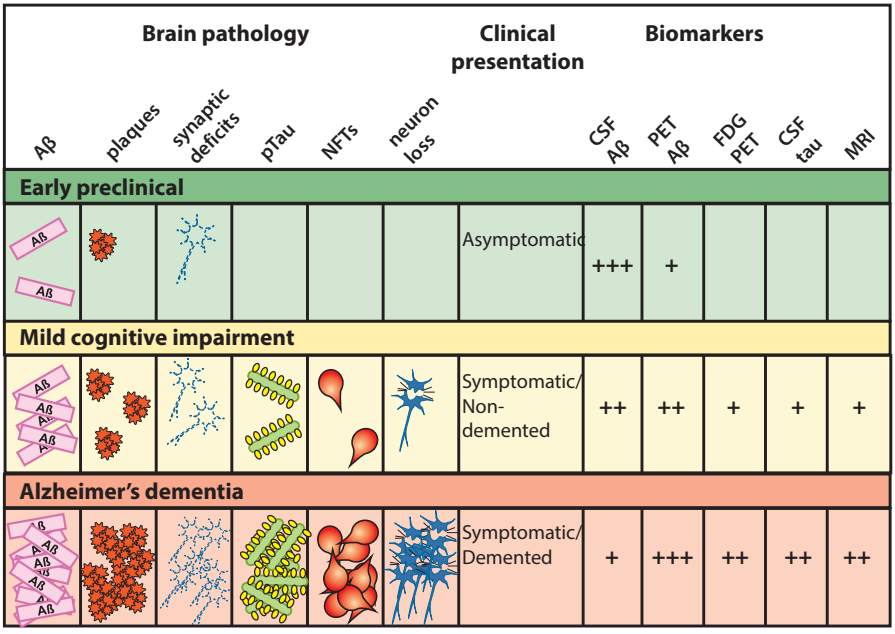

FIGURE 1.37. Alzheimer's pathology may begin decades before the onset of clinical symptoms. As AD pathology progresses, changes in AD biomarkers can also be seen (Albert et al, 2011).

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The Retina as a Window to the Brain

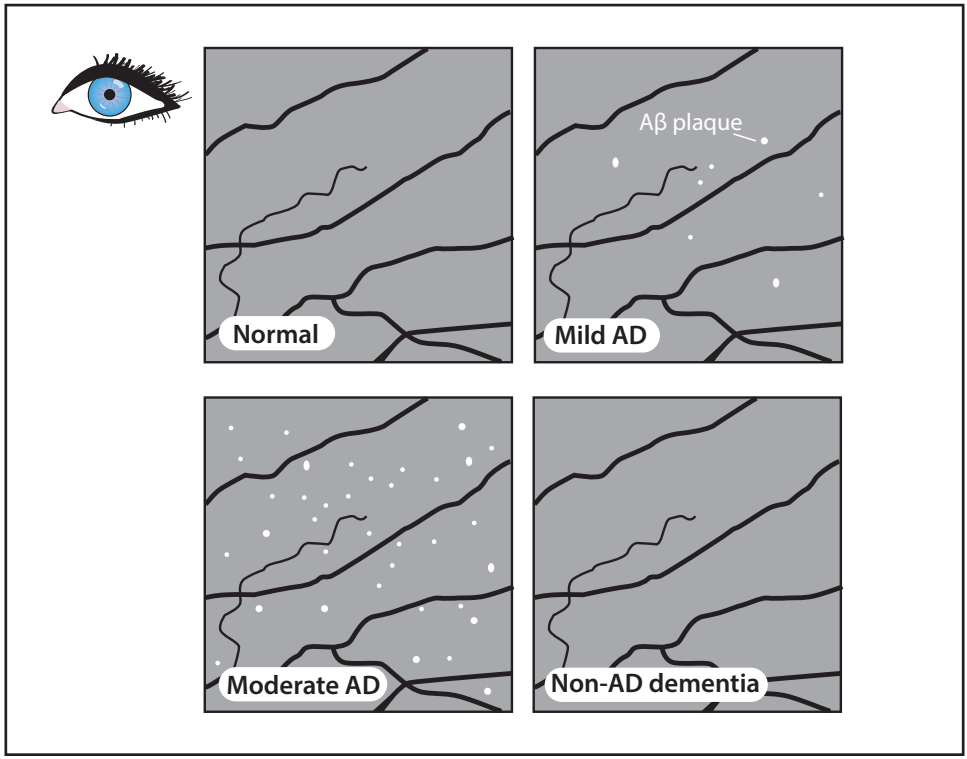

FIGURE 1.38. Given that the retina shares physiological features with the brain, one fascinating technique being developed as a less invasive (compared to CSF, MRI, or PET measures) way to detect AD pathology in the brains of living patients is through retinal imaging. Indeed, it has been shown that curcumin-labeled Aβ plaques can be visualized through retinal scanning and that these retinal plaques correlate well with AD pathology in the brain upon autopsy. Thus, in the near future, this technique may offer a relatively inexpensive method for the early, differential diagnosis of AD that can be easily implemented and performed as part of a routine eye examination (Cheung et al, 2017; Lim et al, 2016; Koronyo et al, 2017).

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Sniffing out Alzheimer's Disease

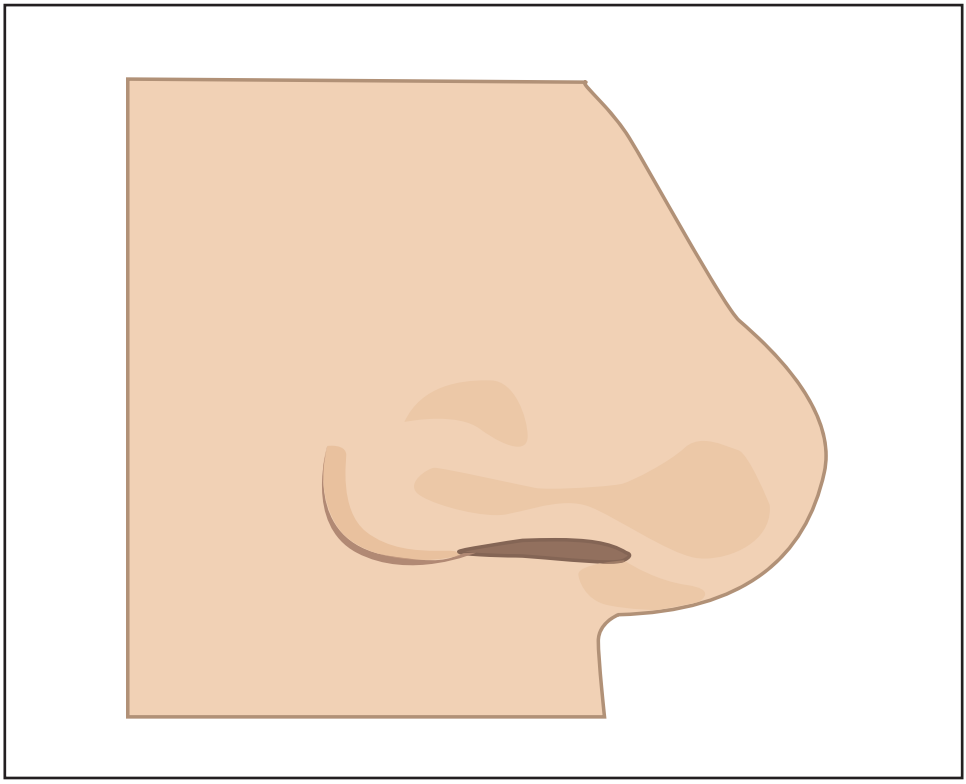

FIGURE 1.39. Deficits in olfaction, especially odor identification, are often robust in patients with mild cognitive impairment (MCI) and may reflect damage to the hippocampus and entorhinal cortex. It has therefore been proposed that olfactory testing may, hypothetically, be used as a non-invasive, fast, inexpensive method to screen for MCI and patients at risk for developing AD (or another dementia where olfactory deficits are also evident, such as dementia with Lewy bodies) (Roalf et al, 2016).

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Does the Presence of Aβ Mean Alzheimer's Disease Is Inevitable?

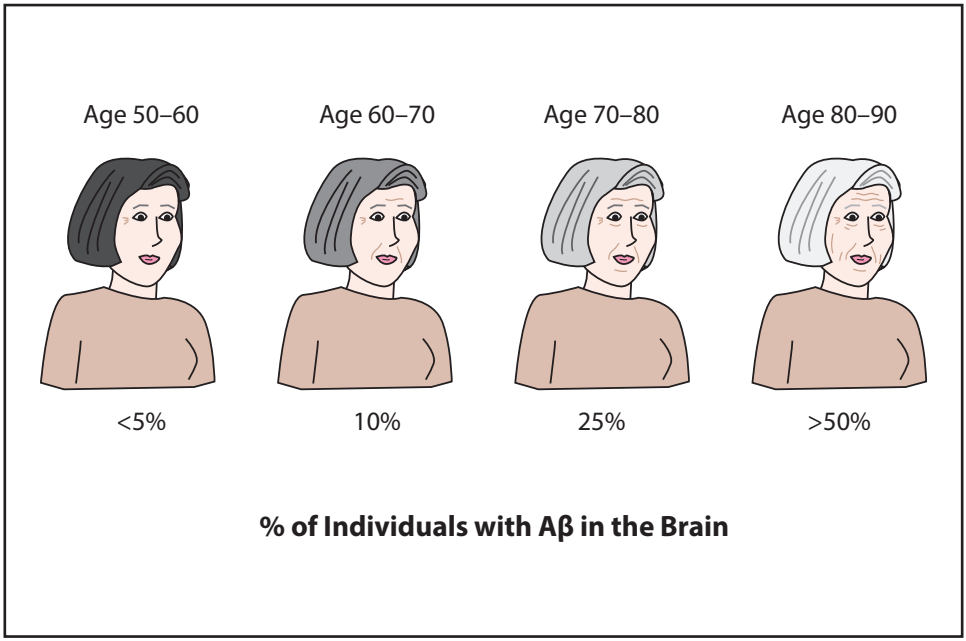

FIGURE 1.40. Not all individuals with Aβ protein detectable in the brain have Alzheimer's disease. Although the presence of Aβ has been associated with slightly poorer cognitive performance, approximately 25–35% of individuals with Aβ accumulation in the brain perform within normal limits on tests of cognition. Some hypothesize that such individuals may be in the preclinical or prodromal phases of dementia and will inevitably develop dementia should they live long enough (Gurnani and Gavett, 2016; Jack Jr et al, 2017; Mallik et al, 2017; Villemagne et al, 2017).

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All-Cause Dementia Diagnosis

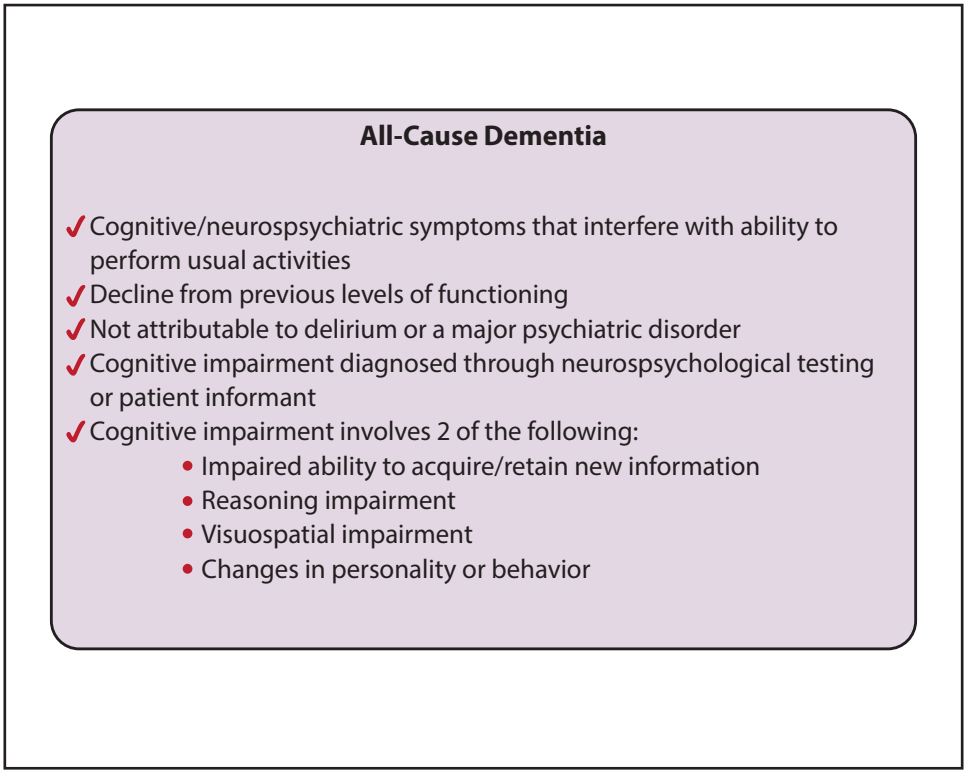

FIGURE 1.41. Dementia can be caused by various pathologies and has differing clinical characteristics; however, all types of dementia share certain clinical features (Grandy, 2012).

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Probable Alzheimer's Disease Diagnosis

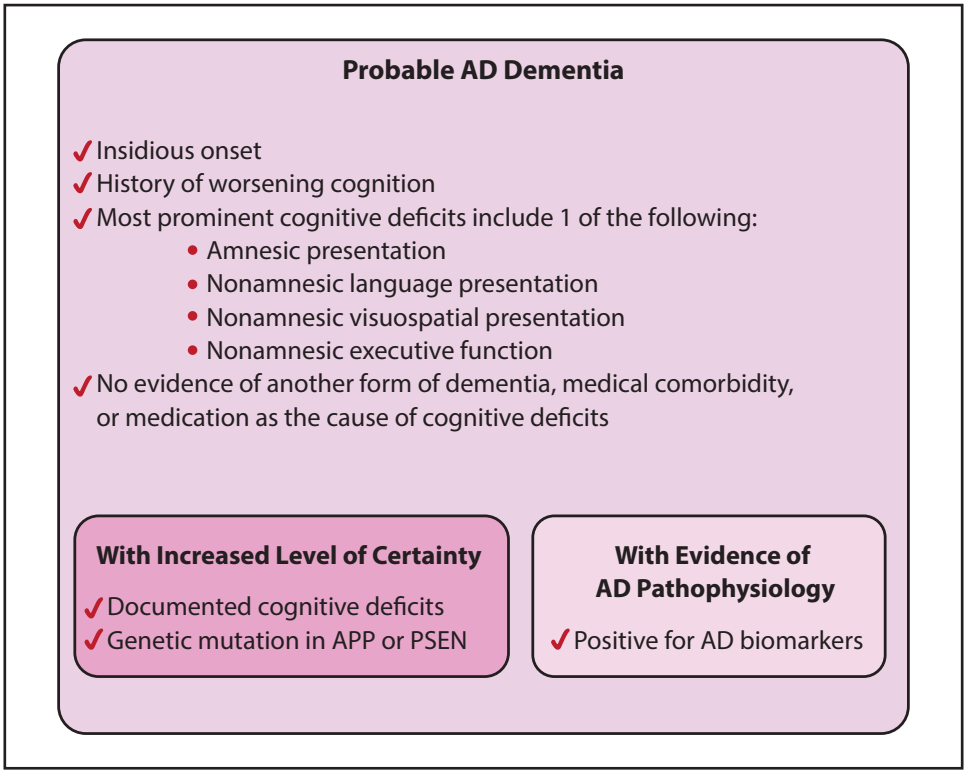

FIGURE 1.42. In 2011, the National Institute on Aging and the Alzheimer's Association released new diagnostic guidelines for Alzheimer's disease that incorporate genetics and biomarker evidence of pathology. Although AD can only be officially diagnosed postmortem, these diagnostic guidelines allow for a differential diagnosis to be made with increasing levels of certainty in living patients. Probable AD dementia is diagnosed when the clinical presentation follows a typical course and can be further supported by biomarker and genetic evidence of AD pathology (Grandy, 2012).

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Possible Alzheimer's Disease Diagnosis

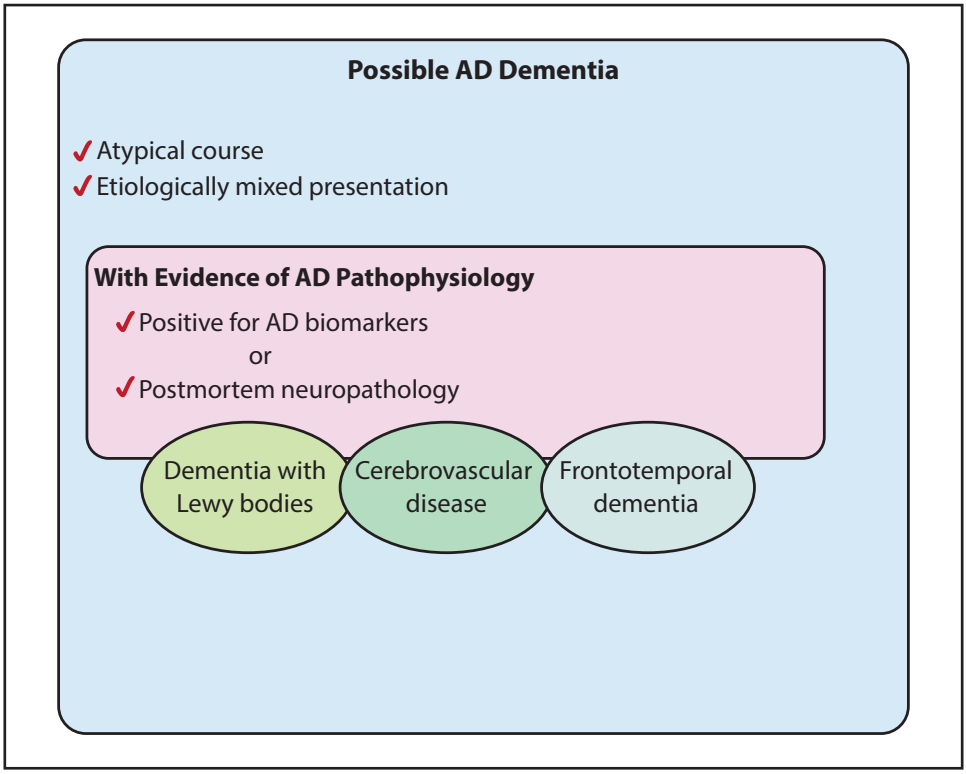

FIGURE 1.43. Often the diagnosis of AD dementia is not clear, typically due to mixed pathological processes contributing to the cognitive dysfunction. In these cases of "mixed dementia," the diagnosis is often possible AD dementia, especially when there is a biomarker or genetic evidence of AD pathology (Grandy, 2012).

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Clinical Progression of Alzheimer's Disease

Early/mild: forgetfulness; short-term memory loss; misplaces items; trouble with complicated tasks; searches for words

Middle/moderate: increased language problem; forgets major events; may need help dressing, cooking; may have a decrease in personal hygiene

Late/severe: verbal communication dwindles; needs help eating, bathing; significant long-term memory loss; decline in motor abilities; does not recognize family members

FIGURE 1.44. As AD progresses, behavioral deficits become increasingly severe and the patient's abilities to complete activities of daily living decline. In addition to the memory deficits and cognitive dysfunction, most patients with AD also exhibit other abnormal neuropsychiatric behaviors such as agitation and psychosis. During the later stages of the disease, patients require round-the-clock care. Alzheimer's disease is typically slow in causing actual death; many patients survive a decade or more with severe AD (Alzheimer's Association, 2017).

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Mild Cognitive Impairment

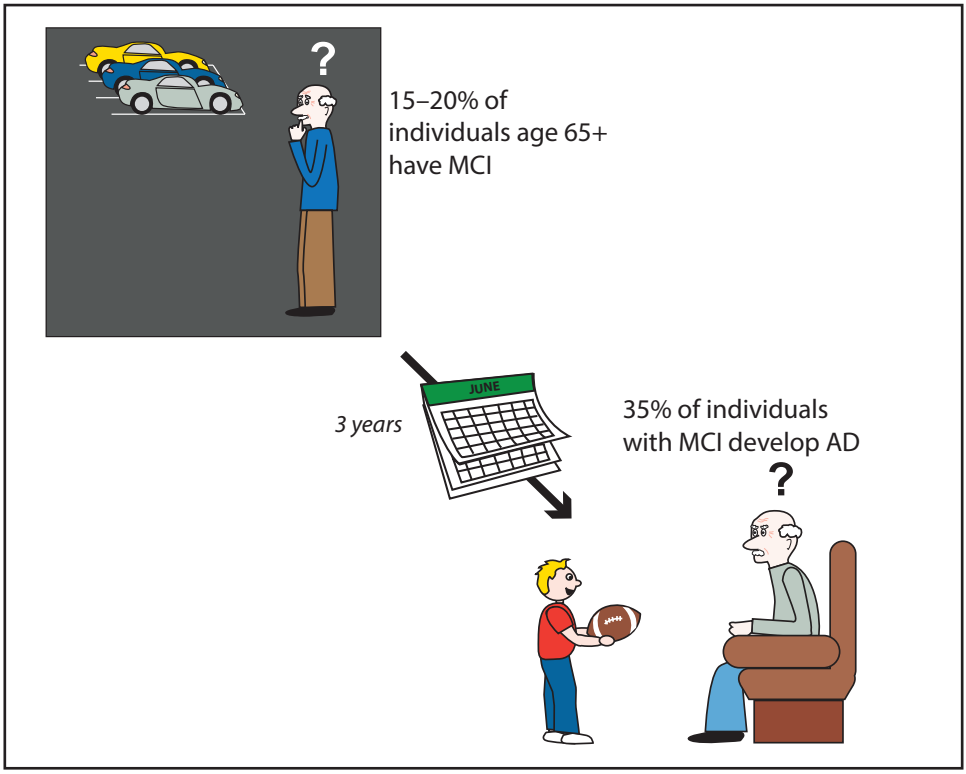

FIGURE 1.45. Mild cognitive impairment (MCI) denotes the presence of mild cognitive decline that does not significantly affect the ability to carry out activities of daily living and does not meet the threshold for dementia. Although MCI is evident in the early, prodromal stages of AD, not all patients with MCI will go on to develop AD and, in fact, many individuals with MCI can return to healthy cognition with proper treatment. For example, patients with a major depressive disorder often present with MCI but, with proper antidepressant treatment, symptoms of MCI often improve or remit. One of the great efforts on the part of Alzheimer's researchers is determining what factors (e.g., positive AD biomarker evidence) might help to predict which patients will progress from MCI to AD (Alzheimer's Association, 2017; Alexopoulos et al, 2016; Allan et al, 2017; Burmester et al, 2016; Herukka et al, 2017; Mallik et al, 2017; Pascoal et al, 2017; Pandya et al, 2016).

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Differential Diagnosis: Clinical Presentation

Normal Aging	AD (Alzheimer's disease)	VaD (Vascular dementia)	DLB (Dementia w/ Lewy bodies)	FTLD (Frontotemporal lobe degeneration)
• Reduced speed of mental processing and choice reaction times • Benign forgetfulness that is mild, inconsistent, and not associated with functional impairment	• Short-term memory loss • Impaired executive function • Difficulty with activities of daily living • Time and spatial disorientation • Language impairment, personality changes	• Impaired abstraction, mental flexibility, processing speed, and working memory • Verbal memory is better preserved • Slower cognitive decline • Dementia occurs within several months of a stroke	• Visual hallucinations • Spontaneous parkinsonism • Cognitive fluctuations • Visuospatial, attention, and executive function deficits are worse • Memory impairment is not as severe • Earlier presentation of psychosis and personality changes • Rapid eye movement (REM) sleep disturbances	• Progressive behavioral and personality changes that impair social conduct (apathy, disinhibition, etc.) • Language impairment • Possibly preserved episodic memory

FIGURE 1.46. The most common causes of dementia, including Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration (FTLD), typically present with clinical symptoms that differ from one another and from the mild cognitive decline often seen in healthy aging. Each of these common forms of dementia is discussed in more detail in subsequent chapters (Tarawneh and Holtzman, 2012; Weintraub et al, 2012; Ritter et al, 2017).

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Differential Diagnosis: Neuroimaging

	AD	VaD	DLB	FTLD
MRI	Medial temporal lobe atrophy	Medial temporal lobe atrophy; white matter abnormalities	Medial temporal lobe atrophy	Medial temporal lobe atrophy
FDG-PET	Temporoparietal cortices	Fronto-subcortical networks	Parieto-occipital and temporoparietal cortices	Frontotemporal cortices

FIGURE 1.47. The most common causes of dementia, including Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration (FTLD), also each have distinct features visible through magnetic resonance imaging (MRI) and fluorodeoxyglucose—positron emission tomography (FDG-PET) (Johnson et al, 2011).

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Short Blessed Test (SBT)	6-item weighted version of the Information–Memory–Concentration Test; usually completed in 5 min; good correlation with AD pathology
Mini-Mental Status Examination (MMSE)	19 items measuring orientation, memory, concentration, language, and praxis; most widely used screening test
Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-cog)	A 20-minute, 70-point scale with 11–14 items that tests memory, language, orientation, and praxis
7-Minute Screen	4 tests (orientation, memory, clock drawing, and verbal fluency)
General Practitioner Assessment of Cognition (GPCOG)	A 6-item screening test similar to the SBT, a clock drawing, and a 5-item informant questionnaire
Montreal Cognitive Assessment (MoCA)	An 8-item, 20-minute evaluation measuring attention, concentration, executive function, language, conceptual thinking, and orientation; 30 points total with 26 or above considered normal
Clinical Dementia Rating (CDR Scale)	A 5-point scale characterizing 6 domains of cognitive and functional performance including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care

FIGURE 1.48. Neuropsychological assessment, including cognitive measures of memory, executive functioning, and activities of daily living, should be done in all patients with suspected dementia in order to aid diagnosis and track disease progression. As such, there is a variety of brief cognitive screening tests available for assessing dementia (Yang et al, 2016; Tarawneh and Holtzman, 2012).

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Currently Available Treatments for Alzheimer's Disease

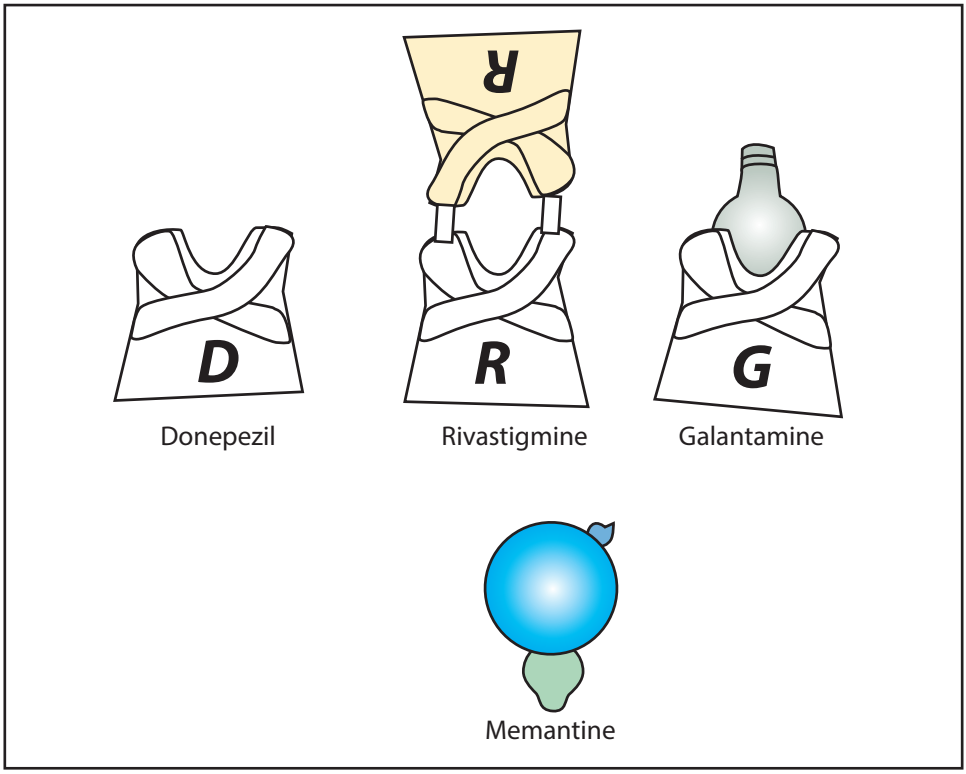

FIGURE 1.49. Available treatments, including the cholinesterase inhibitors donepezil, rivastigmine, galantamine, and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine, may slow progression of AD for a short period of time; however, these existing treatments are ultimately unable to halt progression of the neuronal destruction, memory loss, cognitive deficits, and other neuropsychiatric symptoms of AD (including agitation and psychosis). Although these available treatments provide only moderate symptom relief rather than modifying the clinical course of AD, they can delay institutionalization for up to 2 years. A tremendous effort is underway to find an effective treatment for AD (Stahl, 2013; Geldmacher et al, 2003).

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Cholinergic Neurotransmission

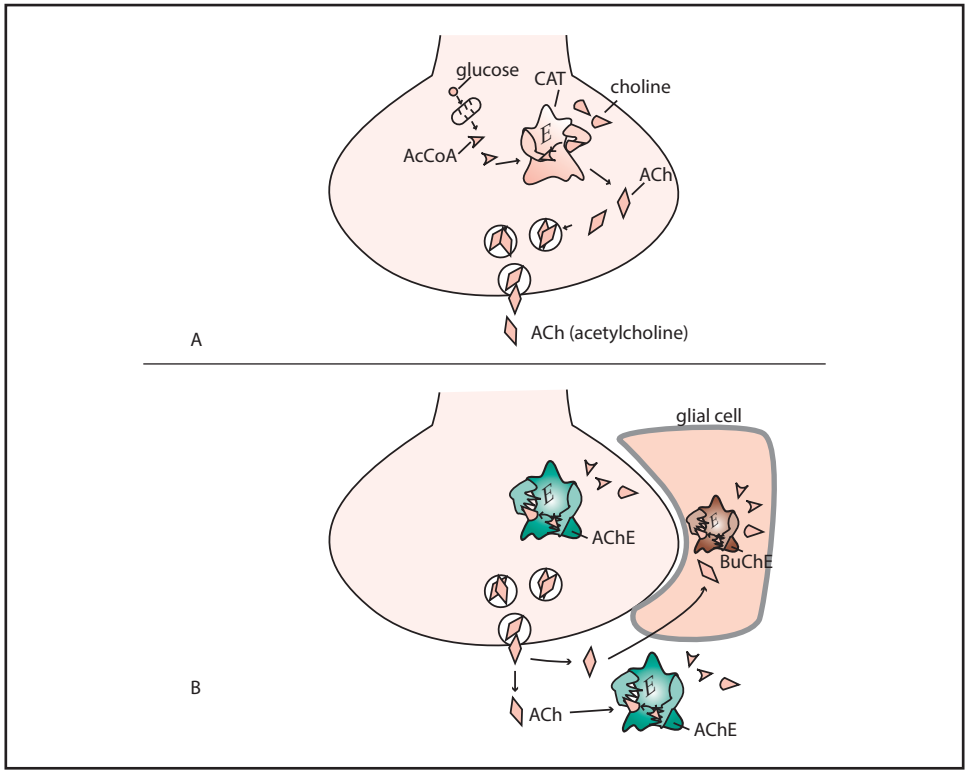

FIGURE 1.50. (A) Acetylcholine (ACh) is formed when two precursors—choline and acetyl coenzyme A (AcCoA)—interact with the synthetic enzyme choline acetyltransferase (CAT). Choline is derived from dietary and intraneuronal sources, and AcCoA is made from glucose in the mitochondria of the neuron. (B) Acetylcholine's action can be terminated by two different enzymes: acetylcholinesterase (AChE), which is present both intracellularly and extracellularly, and butyrylcholinesterase (BuChE), which is particularly present in glial cells. Both enzymes convert acetylcholine into choline, which is then transported out of the synaptic cleft and back into the presynaptic neuron via the choline transporter. Once inside the presynaptic neuron, choline can be recycled into acetylcholine and then packaged into vesicles by the vesicular transporter for acetylcholine (VAChT) (Stahl, 2013).

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Donepezil

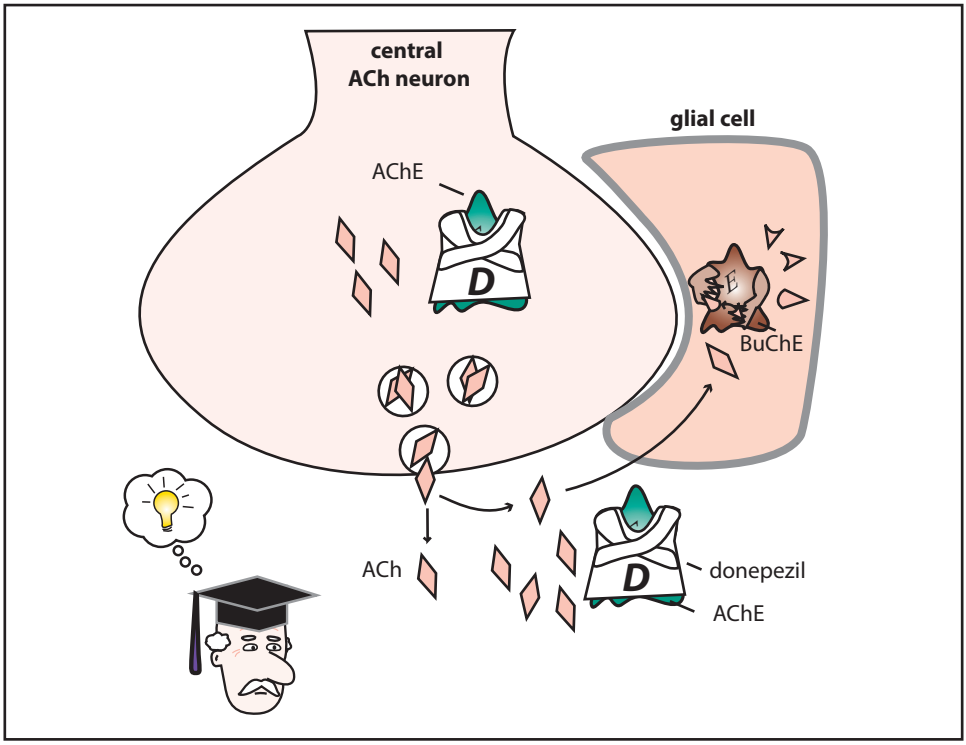

FIGURE 1.51. Donepezil is a reversible, long-acting selective inhibitor of acetylcholinesterase (AChE). It is FDA-approved for the treatment of mild to severe AD and is available as a once-daily formulation. The most notable side effects associated with donepezil are transient gastrointestinal issues. Donepezil inhibits the enzyme AChE, which is present both in the central nervous system (CNS) and peripherally. Central cholinergic neurons are important for the regulation of memory; thus, in the CNS, the boost of acetylcholine caused by AChE blockade contributes to improved cognitive functioning. Peripheral cholinergic neurons in the gut are involved in gastrointestinal effects; thus, the boost in peripheral acetylcholine caused by AChE blockade may contribute to gastrointestinal side effects (Stahl, 2013).

BuChE: butyrylcholinesterase

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Rivastigmine

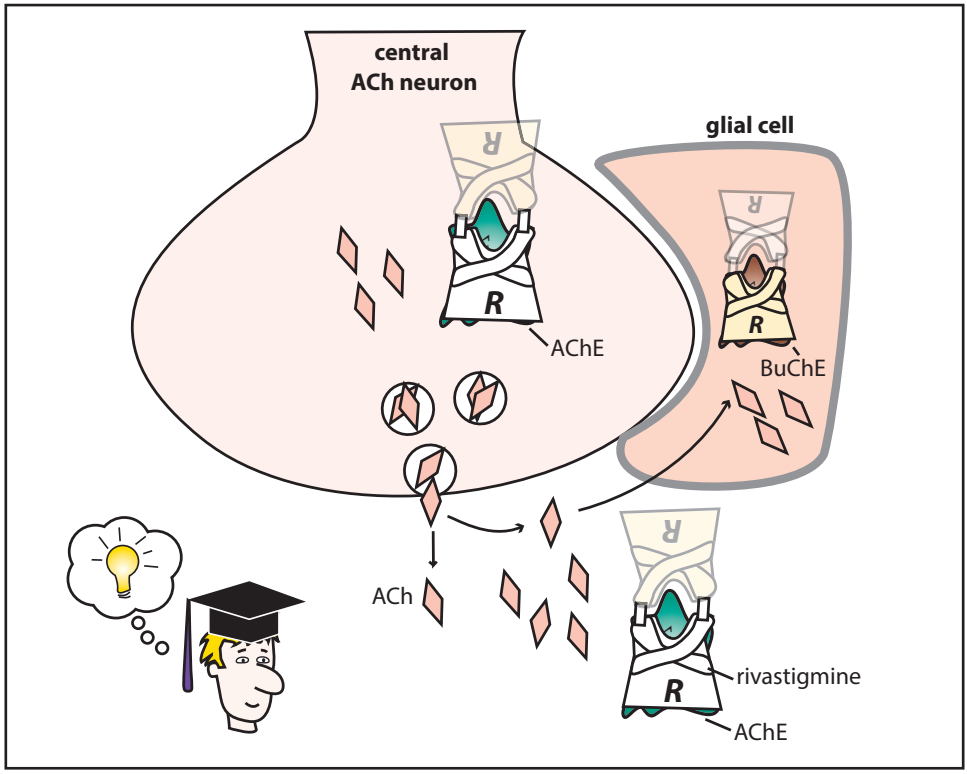

FIGURE 1.52. Rivastigmine is a pseudo-irreversible, intermediate-acting inhibitor of neuronal acetylcholinesterase (AChE) and glial butyrylcholinesterase (BuChE) that is FDA-approved for the treatment of mild-to-moderate AD. In particular, rivastigmine appears to be somewhat selective for AChE in the cortex and hippocampus—two regions important for memory—over other areas of the brain. Rivastigmine's blockade of BuChE in glia may also contribute to enhanced acetylcholine levels. Inhibition of BuChE may be more important in later stages of disease because as more cholinergic neurons die and gliosis occurs, BuChE activity increases. Side effects, most commonly gastrointestinal in nature, can be reduced with the transdermal formulation (Stahl, 2013).

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Galantamine

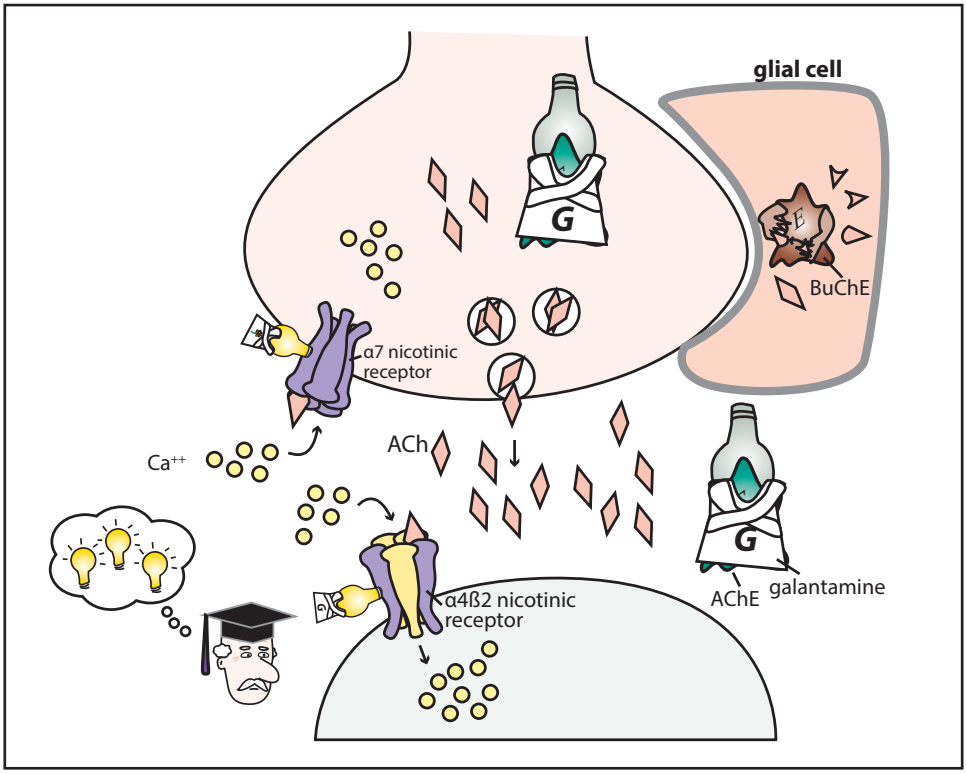

FIGURE 1.53. Galantamine is another acetylcholinesterase inhibitor; however, it is unique among cholinesterase inhibitors in that it is also a positive allosteric modulator (PAM) at nicotinic cholinergic receptors, which means it can boost the effects of acetylcholine at these receptors. Thus galantamine's second action as a PAM at nicotinic receptors could theoretically enhance its primary action as a cholinesterase inhibitor. Galantamine is FDA-approved for the treatment of mild-to-moderate AD and is available in a once-daily formulation (Stahl, 2013).

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Cholinesterase Inhibitors in Practice

Drug	Doses Per Day	BuChE Inhibition	Nausea	Vomiting	Diarrhea	Anorexia
Donepezil	1	-	+	+	+	+
Rivastigmine	2	+	++++	+++	+	++
Galantamine	1 or 2	-	++	++	+	+

FIGURE 1.54. Donepezil is generally used first. Surprisingly, if not effective, another cholinesterase inhibitor (e.g., rivastigmine; galantamine) can benefit the patient in 50% of cases. Thus, therapeutic failure is not a class effect with these drugs (Stahl, 2013; Ohta et al, 2017).

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Glutamatergic Neurotransmission in AD: Part 1

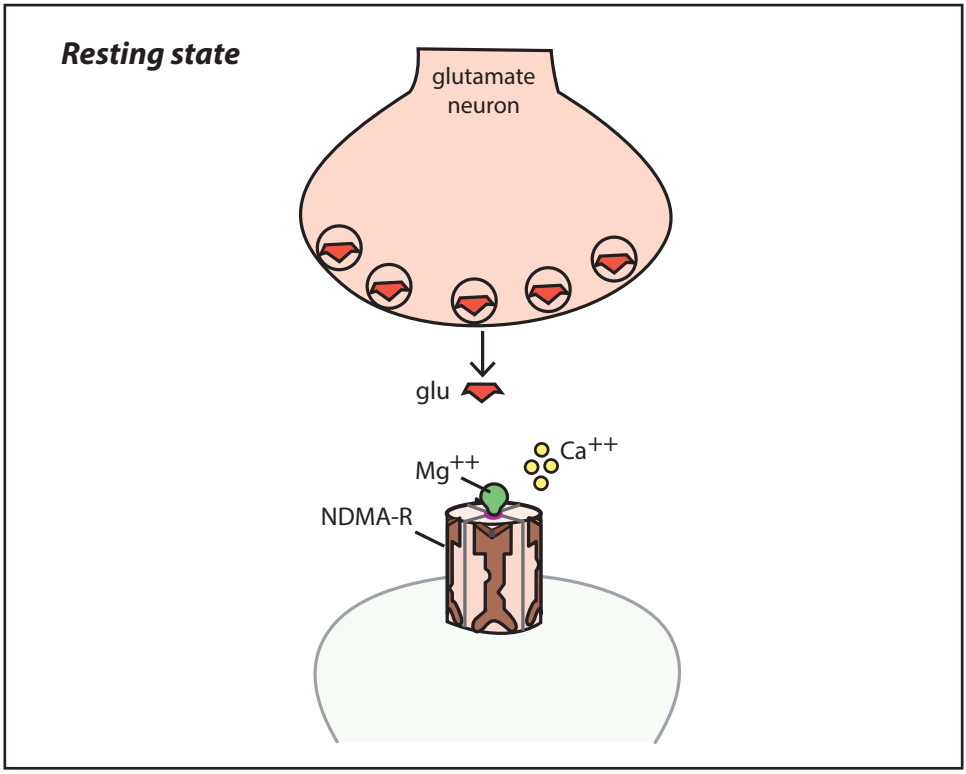

FIGURE 1.55. In the resting state, glutamate is quiet and *N*-methyl-D-aspartate (NMDA) receptors (NMDA-Rs) are blocked by magnesium (Stahl, 2013).

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Glutamatergic Neurotransmission in AD: Part 2

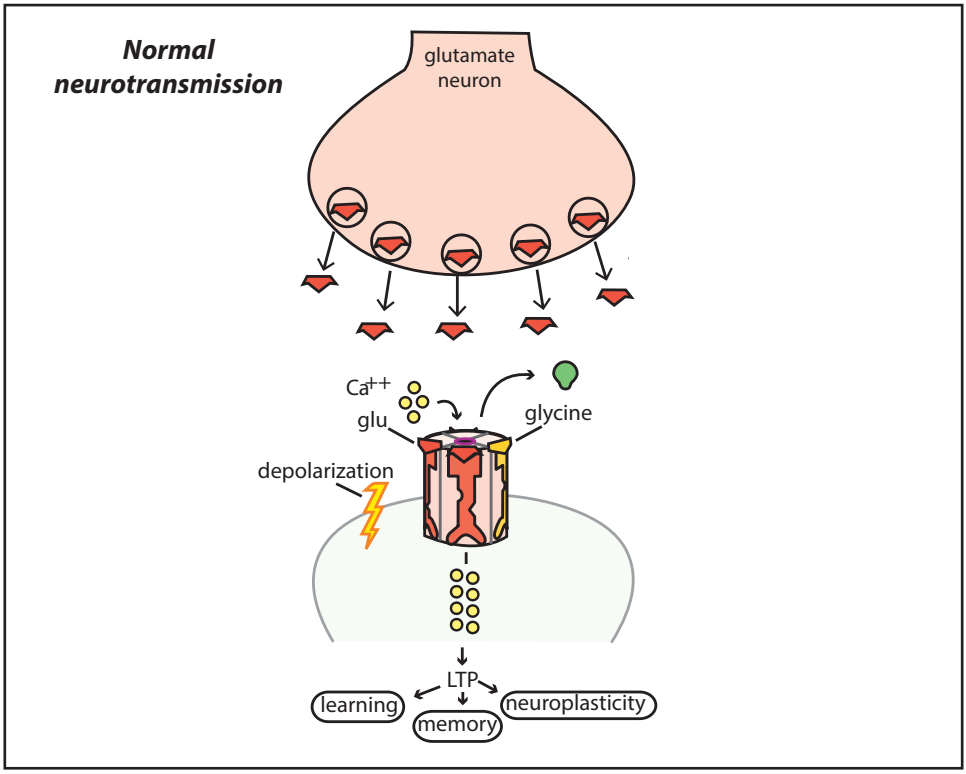

FIGURE 1.56. With normal neurotransmission, glutamate binds to NMDA receptors and, if the postsynaptic receptor is depolarized and glycine is simultaneously bound to the NMDA receptors, the channel opens and allows ion influx (Stahl, 2013).

LTP: long-term potentiation

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Glutamatergic Neurotransmission in AD: Part 3

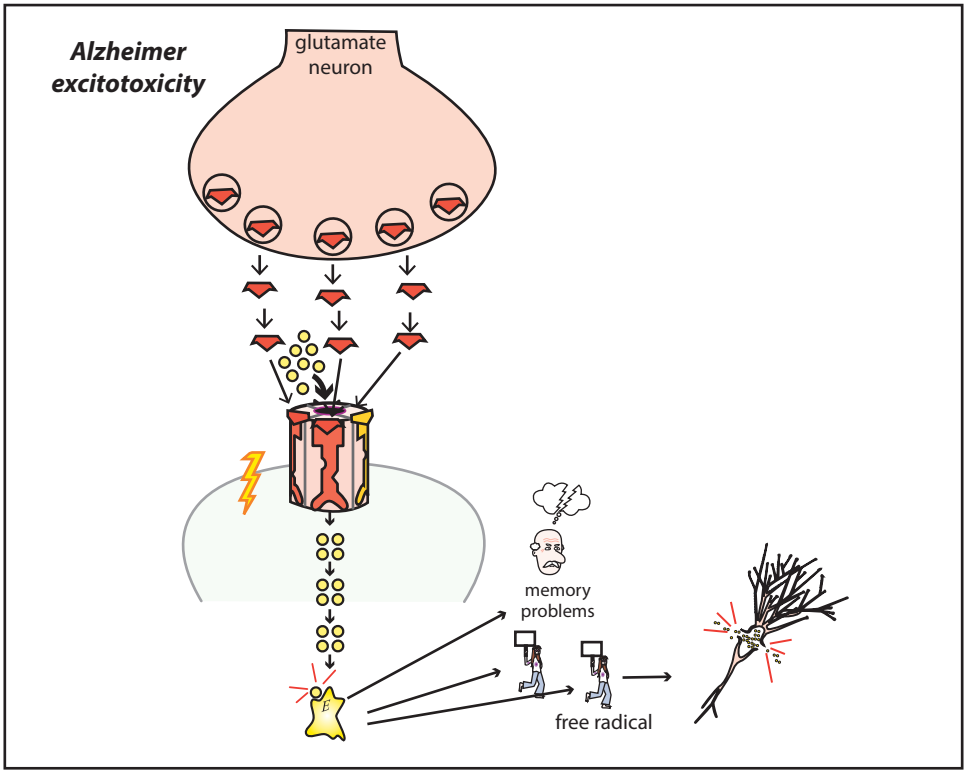

FIGURE 1.57. If amyloid's synaptic effects include downregulating the glutamate transporter, inhibiting glutamate reuptake, or enhancing glutamate release, this could cause a steady leak of glutamate and result in excessive calcium influx in postsynaptic neurons, which in the short term may cause memory problems and in the long term may cause accumulation of free radicals and thus destruction of neurons (Stahl, 2013).

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Glutamatergic Neurotransmission in AD: Part 4

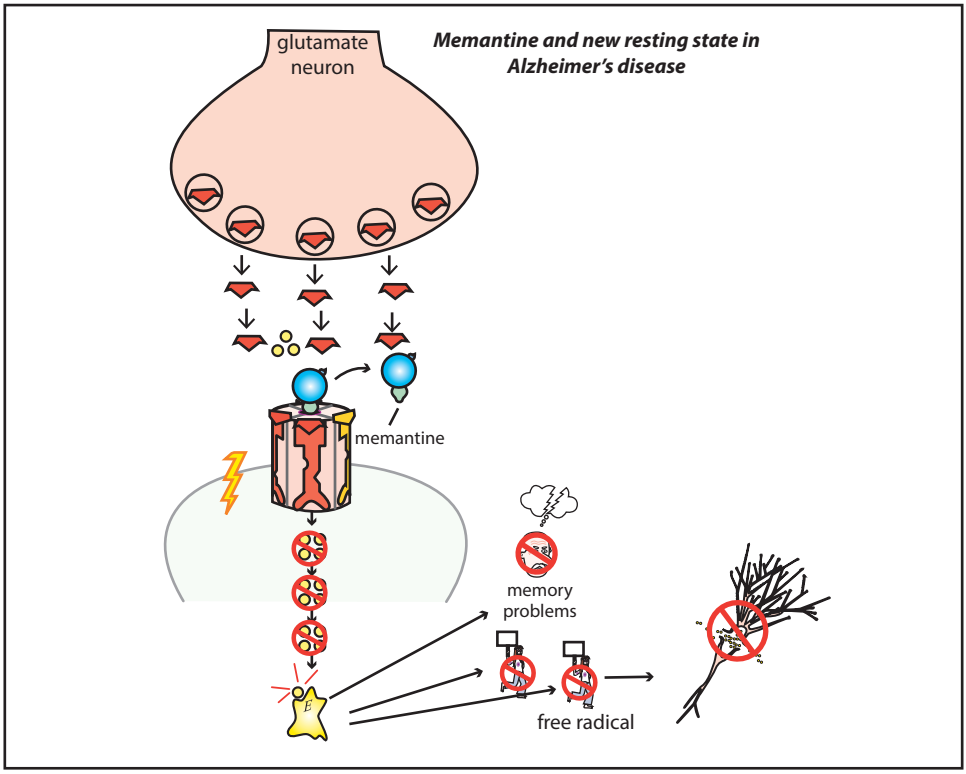

FIGURE 1.58. Memantine is a non-competitive low-affinity *N*-methyl-D-aspartate (NMDA) receptor antagonist that binds to the magnesium site when the channel is open. Memantine blocks the downstream effects of tonic glutamate release by "plugging" the NMDA ion channel and thus may improve memory and prevent neurodegeneration (Stahl, 2013).

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Glutamatergic Neurotransmission in AD: Part 5

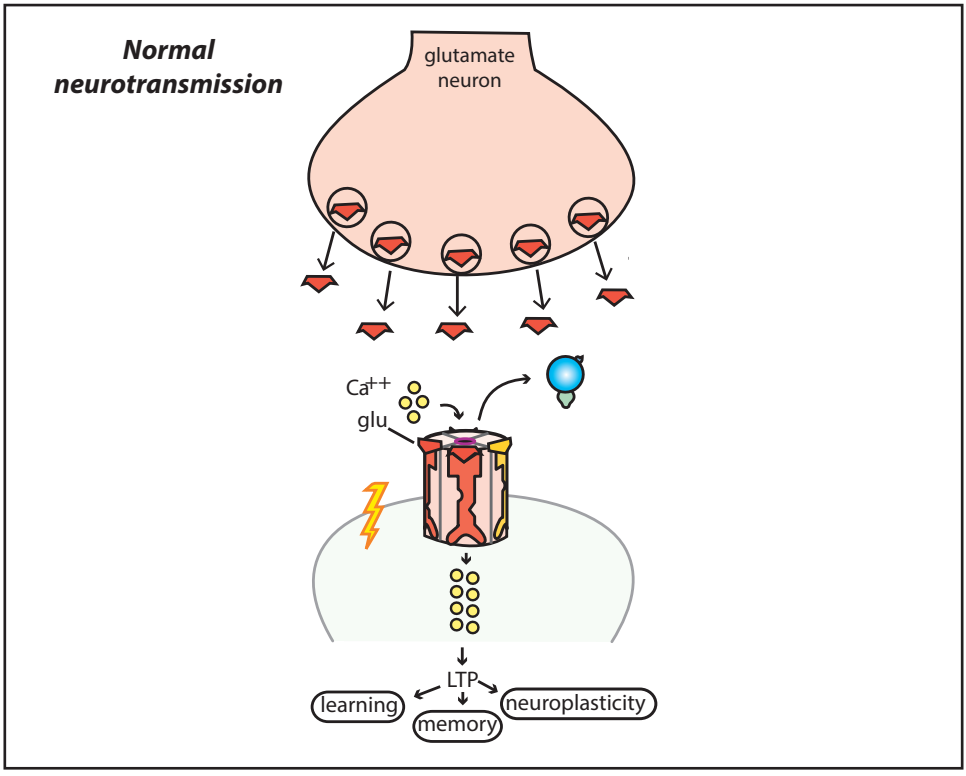

FIGURE 1.59. Memantine has low affinity for NMDA receptors; therefore, when there is a phasic burst of glutamate and depolarization occurs, this is enough to remove memantine from the ion channel and thus allow normal neurotransmission (Stahl, 2013).

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Treatment Algorithm for Alzheimer's Disease

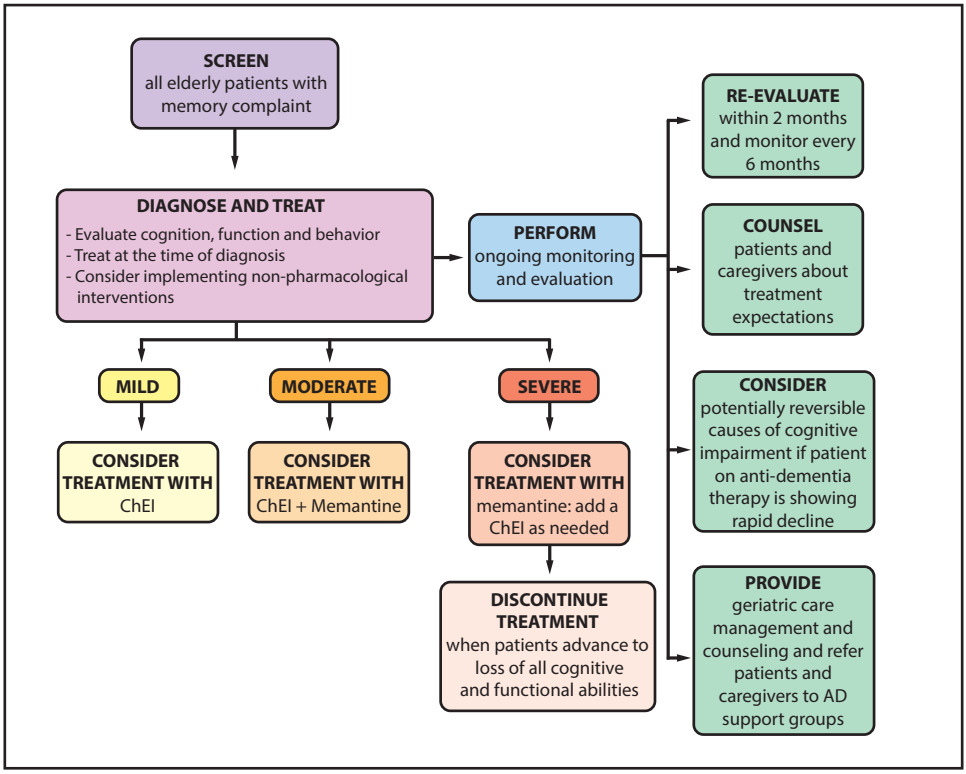

FIGURE 1.60. In addition to pharmacological treatments for Alzheimer's disease, non-pharmacological interventions such as cognitive training, reality orientation, and cognitive stimulation therapy may improve cognitive functioning and quality of life in some patients with AD (Sadowsky and Galvin, 2012; Ballard et al, 2011; Gehres et al, 2016).

ChEI: cholinesterase inhibitor

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Novel Potential Treatments for Alzheimer's Disease

Agents Targeting Aβ Pathology

- Anti-amyloid antibodies
- Active Aβ immunization
- β-secretase inhibitors
- ϒ-secretase inhibitors
- α-secretase promotors
- Aβ aggregation inhibitors

Agents Targeting Tau Pathology

- Anti-tau antibodies
- Active tau immunization
- Tau aggregation inhibitors
- Microtubule stabilizers
- Tau phosphorylation inhibitors

Agents Targeting Metabolic Factors

- Intranasal insulin
- Statins
- Anti-diabetes drugs
- Probiotics

Agents Targeting Inflammation

- COX-2 selective compounds
- Curcumin
- Docosahexanoic acid
- Resveratrol
- Omega-3 and omega-6 fatty acids
- Vitamin E

Agents Modulating Neurotransmission

- Serotonin 5HT6 antagonists
- Histamine H3 antagonists
- 5HT2A antagonists

Others

- RAGE inhibitors
- Calcium channel blockers
- Estrogen

FIGURE 1.61. There are numerous agents currently being studied as potential disease-modifying medications for AD. Primarily, these agents fall into five main categories targeting different aspects of Alzheimer's pathology: amyloid pathology; tau pathology; inflammation; metabolic factors; and neurotransmitter modulation. Some of these novel agents (notably the anti-amyloid antibodies and secretase inhibitors) have made it as far as Phase III clinical testing; however, most of these later-stage trials have failed to show efficacy or have caused side effects serious enough to halt testing. There is a strong consensus that in order for an agent to actually modify Alzheimer's disease course, it will need to be initiated at the very earliest stages of pathology—likely before a patient actually shows any clinical signs of dementia. In this regard, the most recent clinical trials, which employ amyloid and tau biomarkers to detect Alzheimer's disease pathology, may demonstrate more promising results (Arbor et al, 2016; Bronzuoli et al, 2016; Ferrero et al, 2017; MacLeod et al, 2015; Mendiola-Precoma et al, 2016; Panza et al, 2016; Ruthirakuhan et al, 2016; Yan, 2016).

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Passive Immunization with Anti-Amyloid Antibodies

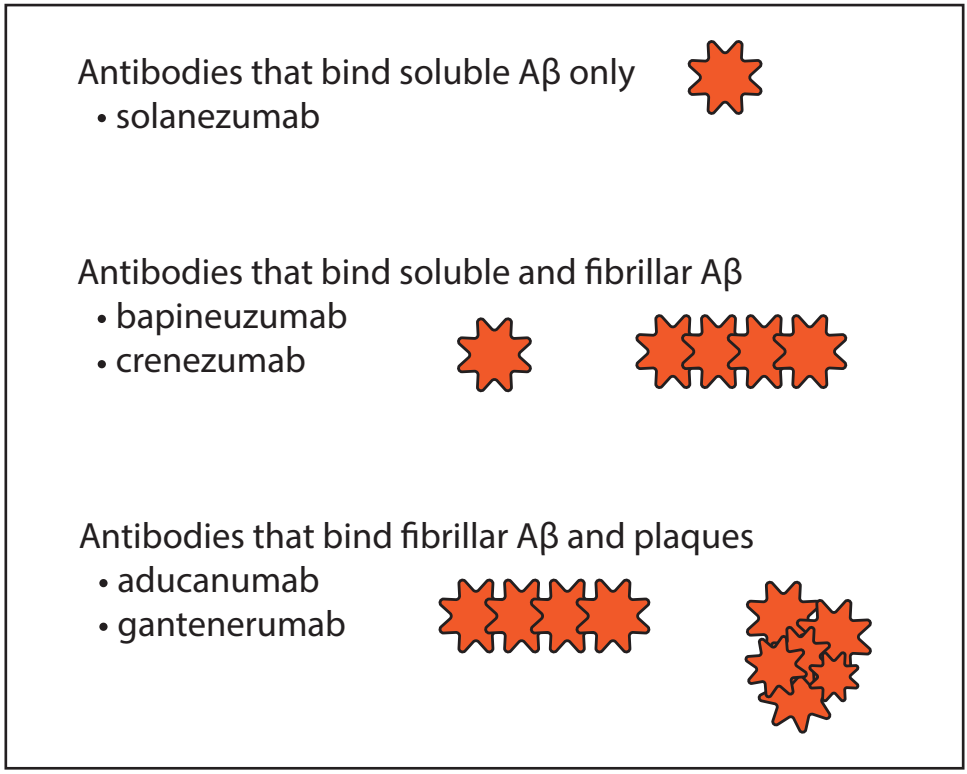

FIGURE 1.62. Antibody-based immunotherapies consist of monoclonal antibodies developed to bind amyloid beta (Aβ) proteins. However, the various anti-amyloid immunotherapies currently in clinical testing are binding to different portions or conformations of the amyloid beta peptide and are thought to remove Aβ from the brain via three hypothesized mechanisms. These mechanisms are peripheral sink; disaggregation; and microglia engagement and phagocytosis. Unfortunately, one issue that has been seen in trials using anti-Aβ antibodies has been the appearance of amyloid-related imaging abnormalities (ARIA) using MRI. These ARIA are thought to represent edema or microhemorrhages caused by the removal of Aβ from blood vessel walls and subsequent leakage of water or blood into the brain (Godyn et al, 2016; Panza et al, 2016; Mallik et al, 2017).

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Anti-Amyloid Antibodies: Phagocytosis

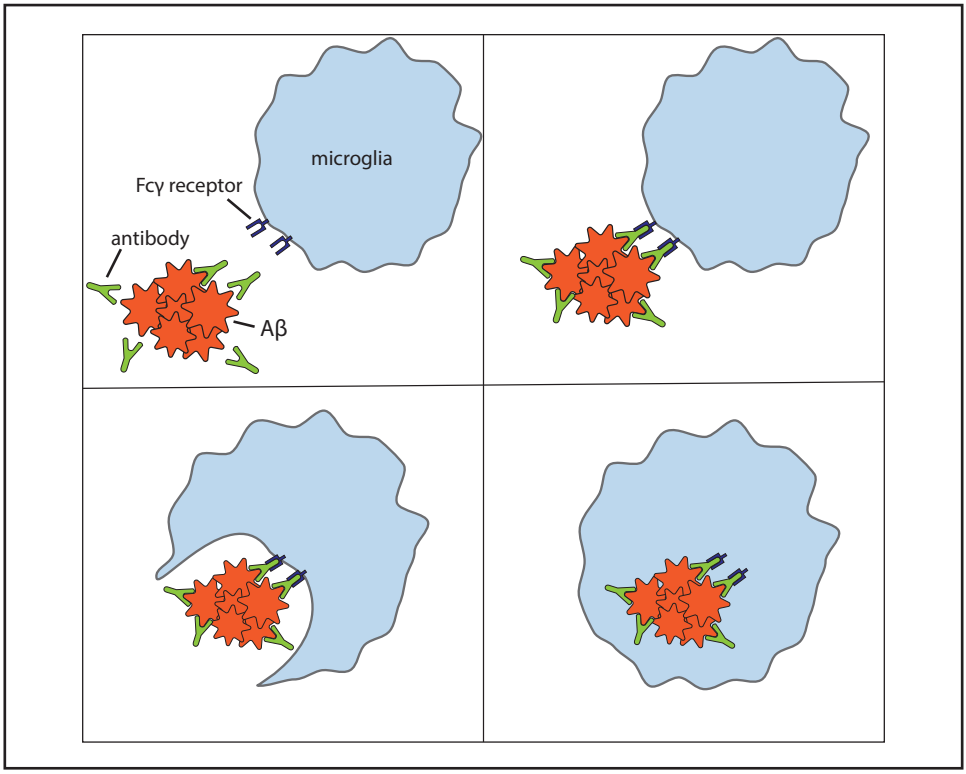

FIGURE 1.63. During microglia engagement and phagocytosis, one portion of the antibody binds to the amyloid beta peptide whereas the Fc portion of the antibody serves as a beacon to call in microglia, the phagocytic cells of the central nervous system. After an antibody binds to amyloid beta protein, Fc-gamma receptors found on microglia bind to the Fc portion of the antibodies. The binding of Fc-gamma receptors to the Fc portion of the antibody causes microglia to engulf amyloid plaques, resulting in the removal of amyloid beta from the brain (Godyn et al, 2016; Panza et al, 2016).

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Anti-Amyloid Antibodies: Peripheral Sink

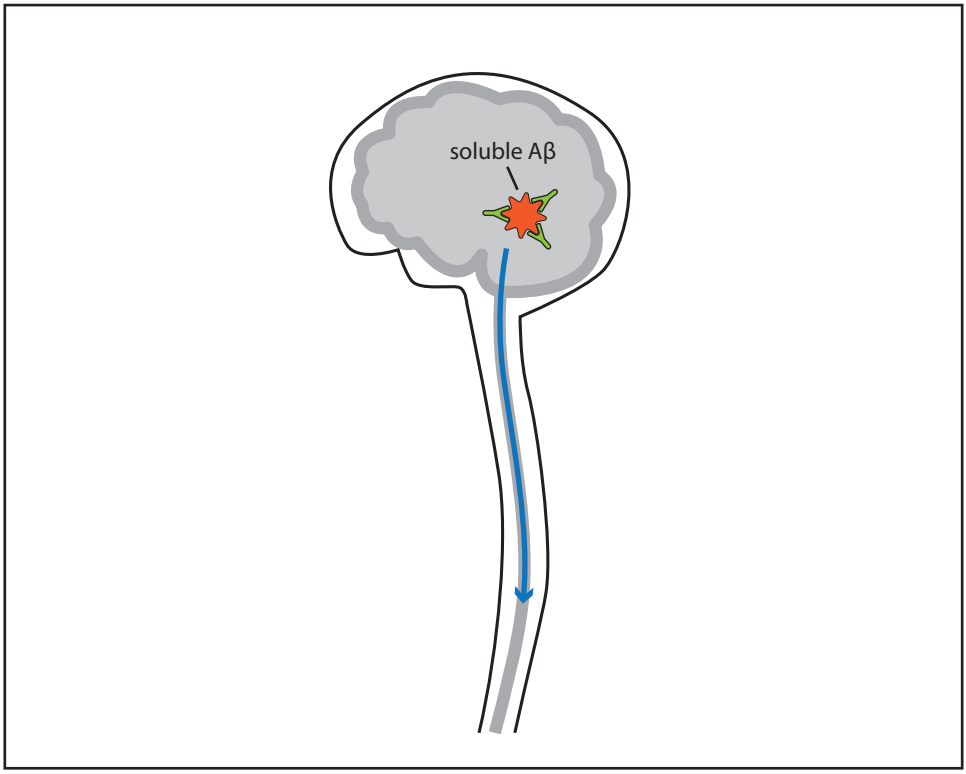

FIGURE 1.64. According to the peripheral sink mechanism, anti-amyloid antibodies bind to the soluble amyloid beta protein before it can aggregate into plaques and cause the removal of that amyloid beta from the brain to the CSF. Consequently, this clearance of soluble, unaggregated amyloid beta hypothetically prevents the growth of amyloid beta plaques (Godyn et al, 2016; Panza et al, 2016).

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Anti-Amyloid Antibodies: Disaggregation

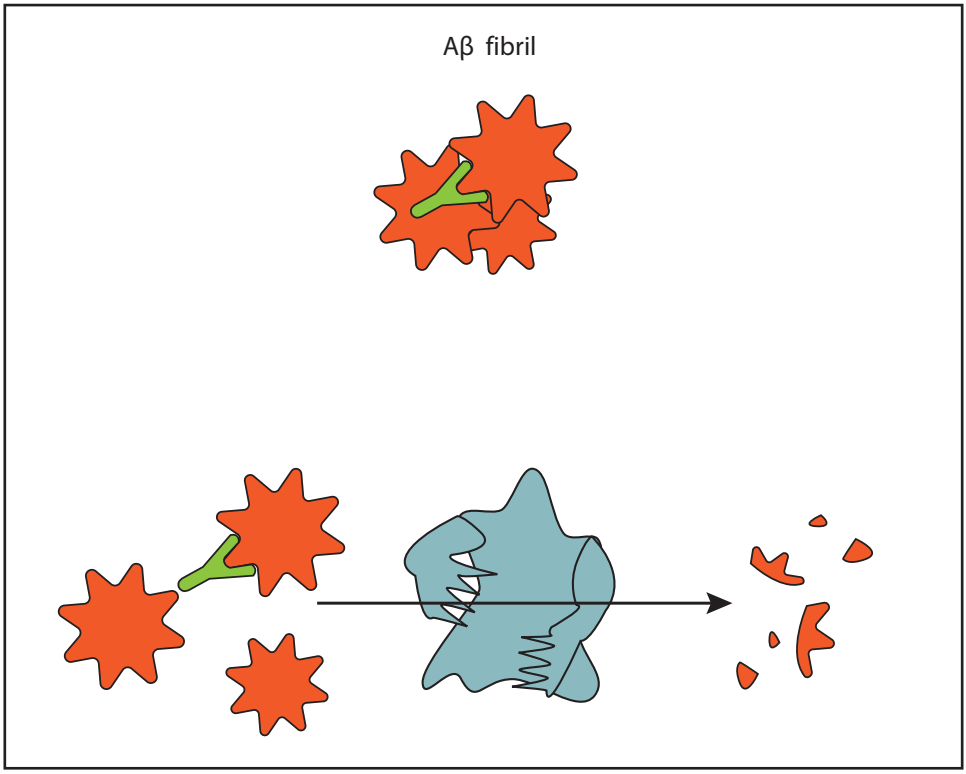

FIGURE 1.65. With the disaggregation mechanism, binding of antibodies to insoluble amyloid beta fibrils causes a disruption of the tertiary structure of the amyloid beta protein. This disruption may hypothetically allow amyloid beta degrading enzymes to access and break down amyloid beta proteins (Godyn et al, 2016; Panza et al, 2016).

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Active Aβ Immunization

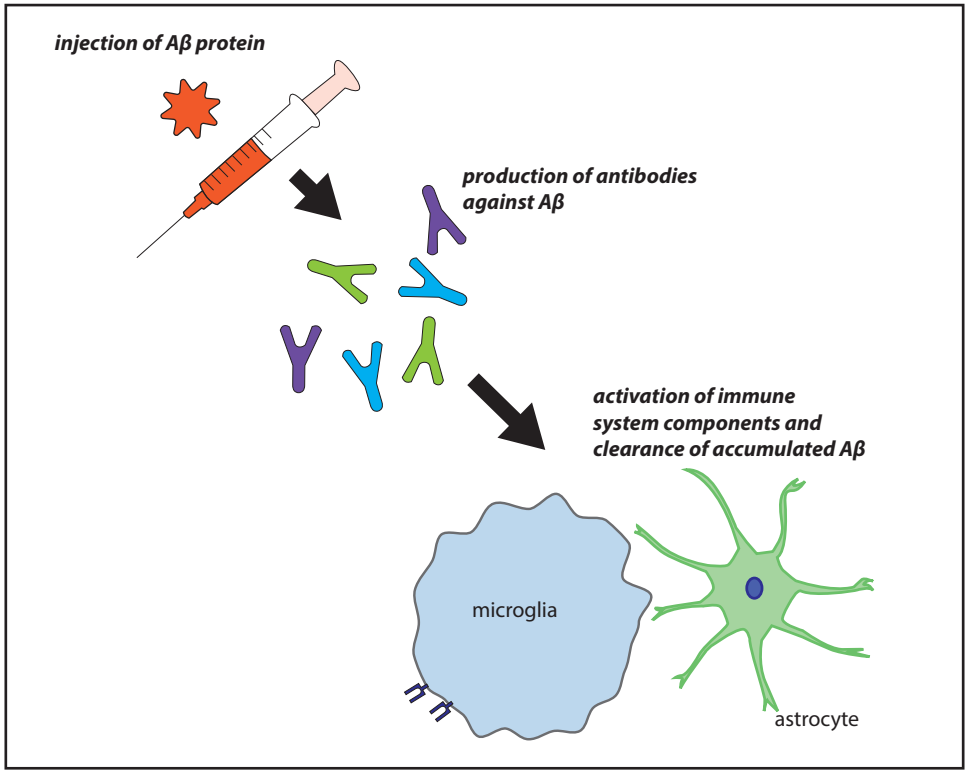

FIGURE 1.66. Active vaccination is another type of immunization that is being investigated for AD. With active immunization, the Aβ protein (either full length or a fragment thereof) is injected, typically with an adjuvant designed to spark the natural immune system. Earliest trials with such vaccines had to be halted due to the induction of severe inflammatory reactions including encephalitis, and many hypothesize that these inflammatory reactions were stimulated by using adjuvants that activated a T-helper cell 1 (Th1) cell response. Th1 immune responses involve more proinflammatory molecules (e.g., cytokines) whereas Th2 cell responses tend to be anti-inflammatory. Researchers are now pursuing Aβ vaccination using Th2-stimulating adjuvants (Wisniewski and Drummond, 2016; Marciani, 2015).

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Alpha-Secretase Promotors

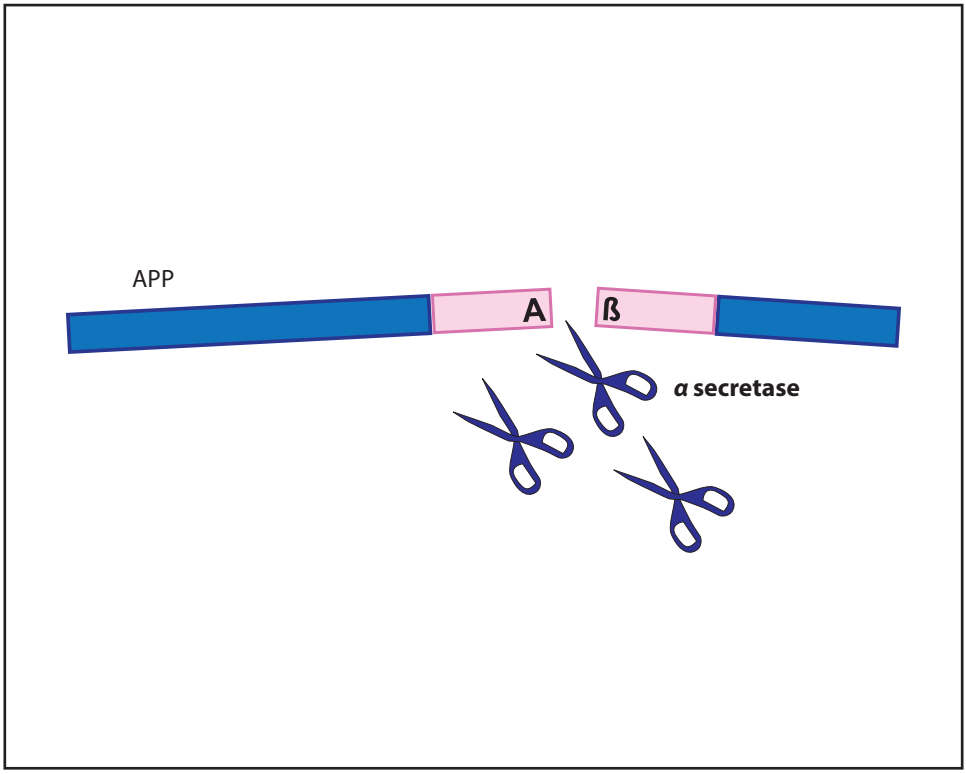

FIGURE 1.67. One potential mechanism for reducing the production of Aβ involves promoting α-secretase cleavage of the amyloid precursor protein (APP). As previously discussed, α-secretase cuts APP within the sequence containing Aβ (i.e., the non-amyloidogenic pathway), thereby precluding the formation of the Aβ peptide. Several agents, including the Monoamine oxidase inhibitor (MAOI) selegiline, the statin atorvastatin, the gamma-aminobutyric acid (GABA) modulator etazolate, the serotonin 5HT4 agonist PRX-03140, the green tea polyphenolic compound epigallocatechin-gallate, the protein kinase modulator bryostatin, and melatonin have been shown to increase α-secretase activity (MacLeod et al, 2015; Mendiola-Precoma et al, 2016).

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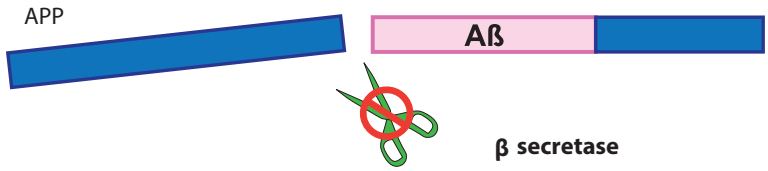
Beta-Secretase Inhibitors



BACE Inhibitor	Clinical Trial Phase
Verubecestat	III
AZD3293	III
E2609	III
CNP520	II / III
JNJ-548611	II / III
CTS21166	I
HPP854	I

FIGURE 1.68. The idea behind using agents that block β-secretase (a.k.a. β-amyloid cleaving enzyme or BACE) is that prevention of cleavage of the amyloid precursor protein (APP) by BACE will inhibit the amyloidogenic APP processing pathway and stop the formation of Aβ protein. Unfortunately, many trials of BACE inhibitors have been halted due to safety concerns, including liver toxicity. The adverse effects of BACE inhibition likely have to do with some of the other processes that BACE is involved in, including muscle spindle formation, myelination, sodium homeostasis, neuronal migration, neurogenesis, and astrogenesis (MacLeod et al, 2015; Ruthirakuhan et al, 2016; Yan, 2016).

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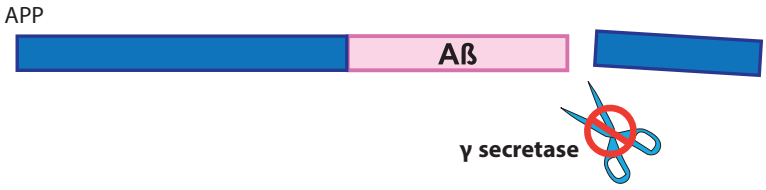
Gamma-Secretase Inhibitors



γ-Secretase Inhibitor	Clinical Trial Phase
Semagacestat	III
Avagacestat	II
EVP0962	II
NIC515	II
γ-Secretase Modulator	**Clinical Trial Phase**
Tarenflurbil	III
CHF5074	II
NIC515	II

FIGURE 1.69. As with BACE inhibition, the idea behind inhibiting γ-secretase is to reduce amyloidogenic processing of APP. Unfortunately, as with many of the BACE inhibitors, most of the studies of γ-secretase inhibitors have been terminated due to safety concerns including skin cancer and the worsening of cognition. In addition to APP, γ-secretase has many other substrates, most notably Notch (a protein important for neurogenesis). Researchers are now working on Notch-sparing γ-secretase inhibitors as well as γ-secretase modulators that may shift γ-secretase processing of APP so that smaller (e.g., Aβ40) rather than larger more toxic (e.g., Aβ42) isoforms are produced (Arbor et al, 2016; MacLeod et al, 2015; Mendiola-Precoma et al, 2016; Ruthirakuhan et al, 2016).

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Targeting Tau Pathology

Tau Vaccination
AADvac1
ACI-35
RG7345
Tau Aggregation Inhibition
Leucomethylthioninium
Methylthioninium chloride
Microtubule Stabilization
TPI-287
Davunetide
Epothilone

FIGURE 1.70. In addition to novel therapies that target production, degradation, or aggregation of Aβ, exploration of many of these strategies is also being directed towards tau protein. Trials with these agents are still primarily in the early phases; however, if successful, such tau-modifying treatments would potentially be applicable in other tauopathies, such as frontotemporal lobar degeneration (Mendiola-Precoma et al, 2016; Panza et al, 2016; Ruthirakuhan et al, 2016).

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Estrogen

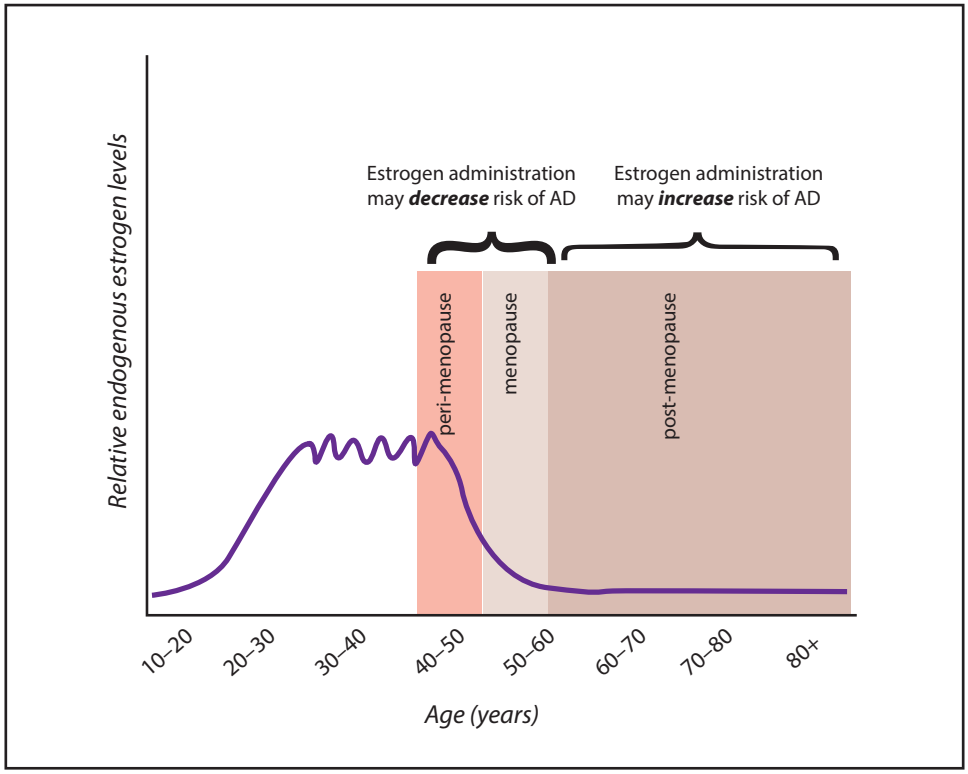

FIGURE 1.71. There are some data, albeit somewhat conflicting, that suggest that estrogen administration in peri- or post-menopausal women may lower the risk of developing AD. However, it appears that the timing of estrogen initiation, as well as apolipoprotein E (APOE) genotype, may be crucial. If delivered during the peri-menopausal phase or shortly after the onset of menopause, estrogen seems protective; however, when administered well after menopause is complete, estrogen seems to actually increase one's risk of developing AD. In terms of APOE genotype, estrogen administration may hypothetically convey the most protection to women who have APOE2 or APOE3 rather than those with APOE4 (Depypere et al, 2016).

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5HT6 Receptors

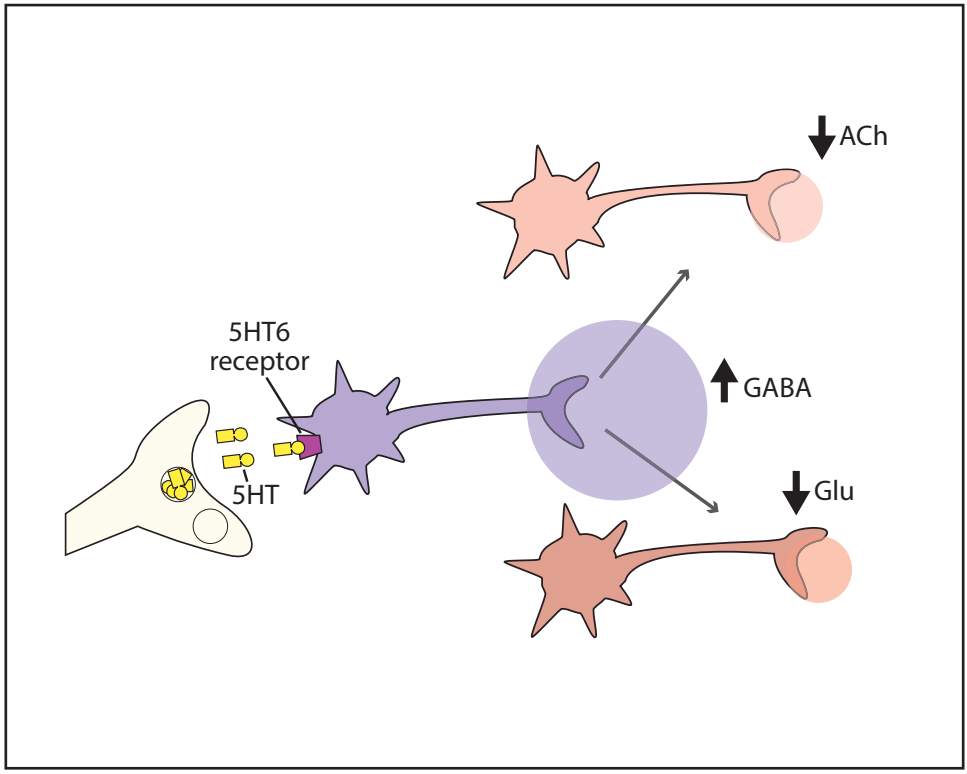

FIGURE 1.72. The serotonin 5HT6 receptor is abundantly located in brain regions associated with memory, including the hippocampus, frontal and entorhinal cortices, nucleus accumbens, and striatum. Binding of serotonin (5HT) to 5HT6 receptors on GABAergic neurons leads to release of GABA on cholinergic (ACh) and glutamatergic (Glu) neurons, causing the inhibition of ACh and Glu release (Ferrero et al, 2017; Atri et al, 2018).

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5HT6 Antagonists

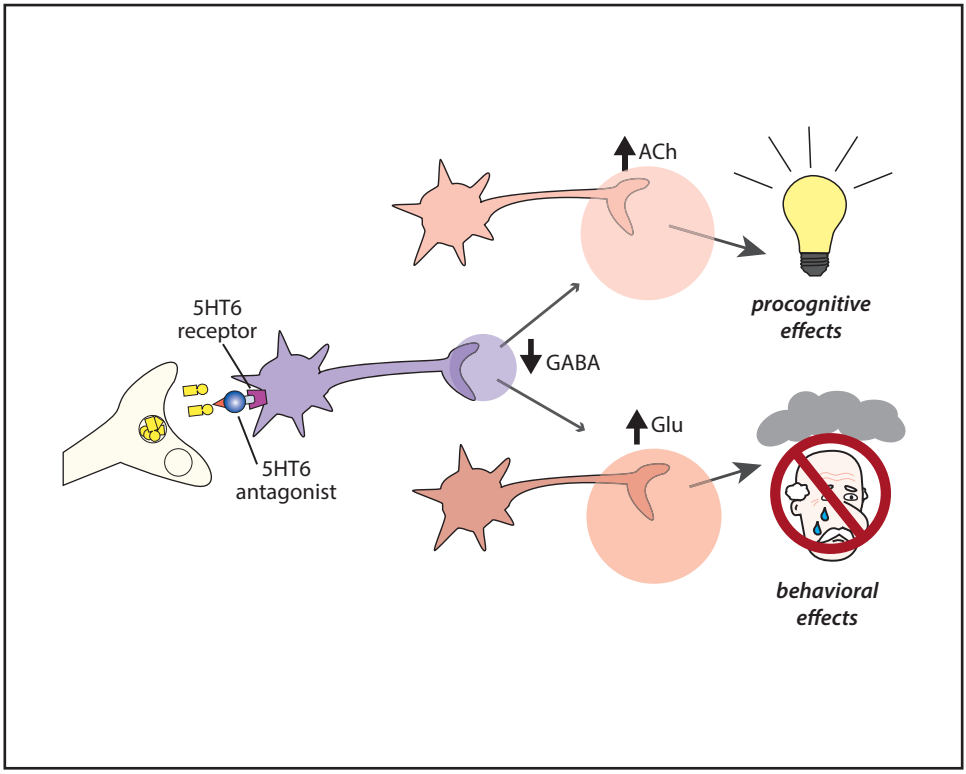

FIGURE 1.73. Antagonism of 5HT6 receptors is hypothesized to lead to disinhibition of both cholinergic (ACh) and glutamatergic (Glu) neurons, thereby improving memory (as well as depression and anxiety—two other frequently exhibited symptoms in dementia). Indeed, agents that modulate the 5HT6 receptor are actively being explored, with some preliminary data suggesting efficacy in improving memory although disappointing results have more recently emerged (Ferrero et al, 2017; Atri et al, 2018).

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