I. INTRODUCTION

Cognitive dysfunction associated with neurodegenerative diseases can occur for many reasons that are not directly associated with any underlying disease process, such as associated with expression of dementia, hormone imbalance, dietary deficiency or excess, drug-induced or heavy metal toxicity, head injury, inherited disorders of the CNS, sleep deprivation, and prolonged stress. All of these causes of cognitive decline are the focus of study. However, because most neurodegenerative diseases are associated with aging, much research has focused on the contribution of normal aging and the changes in vulnerability of selected neurotransmitter systems.

Neuronal dysfunction with aging, particularly with regard to specific neurotransmitter abnormalities, contributes substantially to the development of cognitive symptoms associated with Alzheimer’s disease (AD). Due to the widespread incidence of AD in the aging populations of the world and to the potential financial and societal impacts of finding an effective therapy, the study of AD has motivated and guided the investigation of numerous other age-associated neurodegenerative disorders. The potential impact of targeting
neuronal dysfunction in AD has been advanced by considerable progress in identifying the normal and pathologic mechanisms underlying the degenerative processes that lead to the degeneration of vulnerable neurotransmitter systems within the brain.

Senile plaques and neurofibrillary tangles are two important diagnostic features of AD. Their distribution is not generalized throughout the brain but, instead, demonstrates an intriguing, and thus far unexplained, regional vulnerability. Whether the vulnerability and dysfunction of selected neural systems is a direct result of the degenerative process or simply due to bystander injury is an important question, because the answer can be used to guide the design of an effective therapeutic approach. This chapter reviews the changes that have been observed in the two most vulnerable neural systems associated with AD, the most common and possibly best-studied neurodegenerative disease, and presents the approaches that have been taken to alleviate the symptoms that result from the underlying pathological processes.

II. THE CHOLINERGIC SYSTEM

Acetylcholinergic (cholinergic) neurons in the basal forebrain innervate the cortex and hippocampus and are involved in normal learning and memory and attention (Olton et al., 1988; Wenk, 2003). As a consequence of their vulnerability to aging and the underlying degenerative processes associated with AD, these basal forebrain acetylcholine-releasing neurons may become dysfunctional during the early stages of the disease process (Whitehouse et al., 1981; Davis et al., 1999). The extent to which this neurotransmitter system is impaired may correlate with the severity of selected cognitive symptoms associated with dementia. For example, dysfunction of cholinergic input to the cortex may contribute to a deficit in attentional abilities; alterations in the projection to the central nucleus of the amygdala may underlie emotional changes; and the dysfunction of cholinergic inputs to the hippocampus clearly underlies the presence of amnesia (Olton et al., 1991, 1988; Davis et al., 1999). A deficit in cholinergic biomarkers, including a decline in the level of cholinergic synthetic enzyme, choline acetyltransferase activity, transmitter production and release, and decline in the level of the principal catabolic enzyme, acetylcholinesterase, are commonly reported biochemical changes within the brains of patients with AD (Whitehouse et al., 1981; Davis et al., 1999).

It is important to recognize that the loss of these biomarkers does not herald the death of the cholinergic neuron; an injured neuron will often reduce the production of its luxury systems related to neurotransmitter function in preference to biochemical processes that are essential for recovery. The persistence of these cholinergic neurons offers an opportunity to rescue them from continued degeneration. As such, experimental manipulation of the functional
integrity of cholinergic neurons in the basal forebrain of young rats has been used as an animal model for this component of AD pathology (Wenk et al., 1994; Wenk and Willard, 1999). Moreover, drug therapies designed to attenuate memory deficits associated with AD have focused on alleviating these impairments in the cholinergic synaptic function.

**III. TREATMENT APPROACH: ACETYLCHOLINESTERASE INHIBITORS**

Treatment has focused on reducing the memory impairments by counteracting cholinergic deficits through inhibition of the catabolic enzyme acetylcholinesterase (McGeer et al., 1984; Daiello et al., 2005). The currently available inhibitors of this enzyme, including donepezil, rivastigmine, and galantamine, function by blocking the destruction of released acetylcholine and increasing the life span of the neurotransmitter molecule in the synaptic cleft. This compensates for the reduced production and release of synaptic acetylcholine. However, there is a potential flaw with this therapeutic approach; for example, these enzymatic inhibitors rely on the production and release of acetylcholine from functional cholinergic terminals, and long-term treatment with these acetylcholinesterase inhibitors does not rescue or slow the eventual degeneration of cholinergic cells. Therefore, these drugs rely on the enhancement of synaptic function within a neural system that is actively degenerating, for reasons that are unknown. However, for some AD patients, acetylcholinesterase inhibitors may stabilize cognitive and behavioral function, producing a modest symptomatic benefit that varies between patients, depending on a number of factors, such as age, gender, and the presence or absence of specific genetic mutations (Doody et al., 2003). Approximately 20% of patients given an acetylcholinesterase inhibitor demonstrate a cognitive stabilizing effect that can last up to two years; these findings are consistent with the hypothesis of a potential modifying effect by these drugs on the disease process.

**IV. THE GLUTAMATERIC SYSTEM**

Glutamate is the brain's principal excitatory neurotransmitter, with many physiologic and pathological roles that become important at different stages of life. It is responsible for interneuronal communication in local circuits within virtually every region of the brain and spinal cord and, in many instances, also for communication between distant brain regions. Glutamatergic neurotransmission is critical to normal learning and memory, in part because of its documented role in long-term potentiation and other forms of synaptic plasticity. When the activity of glutamate neurons becomes excessive or the stimulation
of its primary receptors becomes dysfunctional, there are well-characterized pathological consequences, particularly associated with age-related neurodegenerative diseases. Accumulating evidence suggests that the anomalous glutamatergic activity associated with AD may be due to a postsynaptic receptor defect (Rogawski and Wenk, 2003). This defect may be related to an inappropriately timed or sustained glutamate activation of a specific type of glutamate receptor that responds to the agonist N-nethyl-D-aspartate (NMDA), leading to neuronal injury and death (Francis, 2003). Abnormal NMDA receptor function may underlie the selective vulnerability and loss of specific neural systems, ultimately producing cognitive deficits. NMDA receptors are present at many excitatory synapses. They do not contribute to ongoing synaptic transmission because of the unique property that ambient Mg\(^{2+}\) in the extracellular environment blocks them. Mg\(^{2+}\) ions enter the channel and are able transiently to occlude cation flux through the channel by binding to a site deep inside the pore of the channel. At the normal resting potential (e.g., \(-60\) mV) the transmembrane electric field (negative on the inside of the cell) favors entry of Mg\(^{2+}\) into the pore of the receptor so that the channel is blocked. Under such resting conditions, NMDA receptors do not conduct ions. However, with sufficient postsynaptic depolarization within the region of the channel, the neuronal membrane surrounding the channel sufficiently depolarizes so that Mg\(^{2+}\) is no longer strongly attracted into the pore. Under such depolarized conditions, NMDA receptors activated by synaptically released glutamate are able to allow the influx of sodium and calcium ions and contribute to postsynaptic excitation and activation of second messenger systems (Albin and Greenamyre, 1992).

The calcium that enters through the NMDA receptors can act as a messenger for various cellular processes through the activation of calcium-dependent protein kinases. Importantly, the calcium ion entry through NMDA receptors during synaptic excitation is believed to be the critical event that underlies a form of synaptic plasticity called long-term potentiation (LTP). Under the pathological conditions associated with AD, the postsynaptic neuronal membrane near the NMDA channels is chronically depolarized, relieving the Mg\(^{2+}\) block of NMDA receptors. Under these conditions, subsequent activation of NMDA receptors by ordinary glutamatergic synaptic activity could permit a continuous "leak" of calcium ions into neurons, theoretically overwhelming the endogenous mechanisms that regulate calcium ion homeostasis (Choi et al., 1987; Albin and Greenamyre, 1992). Oxidative stress may also result in impaired energy production, possibly leading to impaired function of the membrane ion pumps required for maintenance of the resting potential. In any of these situations, excessive calcium ion influx through NMDA receptors could mediate glutamatergic excitotoxicity by activating a host of calcium-dependent signaling pathways, ultimately leading to neuronal degeneration. In addition, calcium entry through NMDA receptors stimulates nitric oxide pro-
duction through closely associated neuronal nitric oxide synthase. Nitric oxide can react with a superoxide anion to form peroxynitrite, which disintegrates into extremely toxic hydroxyl free radicals that can damage cells in a variety of ways. Therefore, neurons that express NMDA receptors would become selectively vulnerable to normal glutamatergic stimulation. Accordingly, there are a number of reports demonstrating that NMDA receptors are depleted in selected regions of the AD brain (Francis, 2003). For example, acetylcholine neurons express NMDA receptors; this could contribute to the vulnerability of these neurons during the early phases of AD.

V. ROLE OF NEUROINFLAMMATION IN NEURODEGENERATION

Chronic neuroinflammation is a key factor underlying neuronal death and the pathophysiological development of AD (Mrak et al., 1995; Akiyama et al., 2000). Regional inflammatory changes are closely related to the cognitive manifestations of AD (Akiyama et al., 2000). In the brains of AD patients, the entorhinal and frontal cortex inflammatory markers, such as activated microglia, demonstrate a higher correlation with synapse loss than does the number of neurofibrillary tangles (DiPatre and Gelman, 1997) or the degree of deposition of Aβ. The brain of an AD patient expresses a significant and well-organized cascade of immunological changes, and these changes occur very early in the progression of the disease and underlie the progression of atrophy and regional degeneration (Cagnin et al., 2001). Memory impairments in the early phases of AD coincide with the development of inflammation within neuronal populations and regions known to be vulnerable in the brains of AD (Davis et al., 1999). The processes underlying the commencement of the inflammation are not completely understood but lead to a cascade of self-propagating cellular events, including blockade of glutamate uptake by glia (Rothwell et al., 1997), increased release of prostaglandins (Katsuura et al., 1989), and enhanced release of glutamate (Hanisch et al., 1997; Emerit et al., 2004). The consequences of the inflammation can relieve the magnesium ion blockade of voltage-gated NMDA channels, increase nitric oxide levels, both leading to calcium ion flux dysregulation, impaired mitochondrial respiration, oxidative stress, a decline in energy production and membrane depolarization (Chao et al., 1995; Emerit et al., 2004), and initiation of the processes outlined earlier leading to cell death (Albin and Greenamyre, 1992; Chao and Hu, 1994).

The consequences of long-term, low-level brain inflammation may lead to a destabilization of neuronal calcium ion homeostasis and further alter intracellular signal-transduction cascades (Barry et al., 2005). The amplitude of the calcium ion entry through NMDA channels, the kinetics of calcium ion release
from intracellular stores, the decay in its free cytoplasmic levels, and the spatiotemporal pattern of activation of NMDA channels distributed around the neural networks within the hippocampus are the principal means by which calcium ion signals are deciphered into a meaningful biological response that can lead to the consolidation of a new memory. NMDA receptor dysregulation is likely to be most evident within brain regions showing the highest degrees of inflammation.

The general neuronal dysfunction that develops as a consequence could impair the mechanisms underlying synaptic plasticity, such as LTP, ultimately leading to memory impairments and neurodegeneration. Therefore, taken together, these findings suggest that neuroinflammation plays an intermediary role in the neurodegenerative processes during the early phases of AD, ultimately contributing to the neuropathology that develops in later stages of the disease (Eikelenboom et al., 1998; Mrak et al., 1995; Wenk et al., 2000b). The mechanisms outlined in this hypothesis predict that an NMDA channel antagonist could enter the pore of the channel and prevent the influx of excessive amounts of calcium ion and attenuate the consequences of the calcium flux dysregulation.

Chronic neuroinflammation may be responsible for the selective vulnerability of neurons in AD. Using an animal model of chronic brain inflammation (Hauss-Wegrzyniak et al., 1998), we have systematically examined, and then selectively inhibited, each step in the cascade shown next that leads to excessive stimulation of NMDA receptors and cell death (Wenk et al., 2000b; Wenk and Willard, 1999; Willard et al., 2000). Many of the components of this cascade are represented by this equation:

\[
\text{LPS} \rightarrow \text{Cytokines} \rightarrow \text{Prostaglandins} \rightarrow [\text{Glutamate}]_{ext} \rightarrow \\
\text{NMDA(R1)} \rightarrow \text{Ca}^{++} \text{ influx, NOS} \rightarrow \text{NO} \rightarrow \\
\text{Dysfunction or Cell Death}
\]

In the current animal model, we used an infusion of lipopolysaccharide (LPS) to generate the inflammation. However, the inflammatory processes may be initiated naturally in the human brain by a diverse array of stimuli that are deposited in response to underlying genetic mutations or inappropriately processed proteins (Akiyama et al., 2000; Francis, 2003). Following the infusion of LPS, activated microglia can indirectly potentiate glutamate-mediated neurotoxicity via the production of prostaglandins, nitric oxide (Morimoto et al., 2002), and cytokines (Bernardino et al., 2005). The inflammatory processes produce a dysregulation in calcium influx via NMDA receptors that could produce multiple unstable conditions, for example, an elevation in intracellular levels of calcium in a larger-than-usual proportion of neurons or a dramatic increase in the number of neurons, with a disruption in neuroplasticity or leading to cell death (Soliven and Albert, 1992). Given the critical
role of NMDA receptors in this cascade, it is not surprising that chronic neuroinflammation leads to a significant decline in the number of NMDA(R1) receptors (Rosi et al., 2004). As predicted by this hypothesis, the greatest receptor loss occurred in those regions of the hippocampus that also had the greatest concentration of activated microglia. Therefore, these results are consistent with the hypothesis that a loss of NMDA receptors in hippocampal regions in response to the presence of chronic neuroinflammation may contribute to the cognitive deficits observed in AD during the earliest phases of the disease (Akiyama et al., 2000; Eikelenboom et al., 1998).

VI. EFFECT OF NEUROINFLAMMATION ON CHOLINERGIC FUNCTION

Neuroinflammation within the basal forebrain selectively destroys acetylcholine neurons in a time-, but not dose-, dependent manner (Wenk et al., 2000a, 2000b; Willard et al., 1999, 2000). Medial septal cholinergic neurons that innervate the hippocampus may also be selectively vulnerable to immune-mediated processes (Kalman et al., 1997). In addition, the level of cholinergic biomarkers was significantly reduced within the septal cholinergic neurons of transgenic mice that express elevated levels of the cytokine tumor necrosis factor-alpha (TNF\(\alpha\); Aloe et al., 1999). Therefore, the entire forebrain cholinergic system may be vulnerable to elevated levels of inflammatory proteins, particularly TNF\(\alpha\) (Wenk et al., 2000b; Willard et al., 1999, 2000). Stimulation of TNF\(\alpha\) receptors may induce cell death by "silencing of survival signals" via the inhibition of insulin-like growth factor-1-mediated signaling within neurons (Venters et al., 2000). TNF\(\alpha\) can also inhibit glutamate reuptake into astrocytes and may potentiate glutamate receptor-mediated toxicity (Soliven and Albert, 1992; Chao and Hu, 1994; Chao et al., 1995; Probert et al., 1997) within the basal forebrain, a region that is vulnerable to excess glutamatergic function (Kim and Ko, 1998).

Although the mechanism underlying the degeneration of basal forebrain cholinergic cells is unknown, the specificity of these effects on cholinergic neurons was initially suggested by a study that isolated antibodies from the sera of AD patients that selectively recognized and destroyed basal forebrain cholinergic cells when injected into a rat brain (Foley et al., 1988). In addition, head trauma in humans is a significant risk factor for AD (Rasmusson et al., 1995) and is associated with increased levels of inflammatory proteins (Griffin et al., 1994) and a decline in the number of basal forebrain cholinergic neurons (Murdoch et al., 1998). In vitro studies also indicate that brain inflammation may selectively destroy basal forebrain cholinergic neurons (McMillian et al., 1995).
VII. TREATMENT APPROACH: ANTI-INFLAMMATORY THERAPY

Current treatments for AD as well as many other neurodegenerative diseases typically provide only moderate symptomatic benefits and do not modify the progression of disease. The inflammatory process represents a target for potential disease-modifying drugs that may influence multiple critical steps in the pathogenesis of AD, such as glial activation and production of cytokines and complement proteins (Andersen et al., 1995; Stewart et al., 1997). Results from clinical trials have increased insight into the potential mechanisms of action of multiple nonsteroidal anti-inflammatory drugs (NSAIDs). For example, some NSAIDs may lower the amyloid burden without affecting other important physiological pathways. Epidemiological evidence provides strong support of the chronic use of NSAIDs for reducing the risk of AD (Andersen et al., 1995) and slowing the cognitive decline (Breitner et al., 1994; McGeer et al., 1990; McGeer and McGeer, 1998; Wyss-Coray and Mucke, 2000). Investigators have found a significant association between exposure to NSAIDs for more than two years and AD risk reduction (Breitner et al., 1994). Recent studies suggest that although anti-inflammatory agents do not appear to slow progression of dementia, they may have a preventative influence on the development of AD pathology (Breitner et al., 1994; Wenk et al., 2000b; Marchetti and Abbracchio, 2005). However, multiple clinical trials have elicited mixed (Rogers et al., 1993; In ‘T Veld et al., 2001), albeit mostly negative, results (McGeer et al., 1990). Additional work to evaluate their potential protective properties further is warranted.

VIII. TREATMENT APPROACH: GLUTAMATE CHANNEL ANTAGONISM

Although the basis of the vulnerability of cholinergic neurons in AD is not understood, one possibility is that the degeneration of these neurons might be due to inappropriate activation of the NMDA receptors they express (Wenk et al., 1994, 1995, 1997; Muir, 1997). Indeed, infusion of NMDA or glutamate receptor agonists such as quinolinic acid into the rodent basal forebrain region is associated with a loss of cholinergic neurons, as demonstrated by a decrease in the release of acetylcholine in the projection regions and a decline in the activity of choline acetyltransferase. Furthermore, the loss of these neurons, due either to the infusion of NMDA or the presence of chronic neuroinflammation, is associated with impaired spatial memory. Antagonism of the glutamatergic channel function has become a potential target for novel pharmacotherapies. For example, memantine is an uncompetitive, low-affinity NMDA-receptor antagonist. It is believed to have an impact on the abnormal
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Glutamatergic process associated with AD by selectively blocking the excitotoxic effects of atypical glutamate transmission while allowing normal physiological function to occur (Rogawski and Wenk, 2003). Memantine binds deep inside the NMDA receptor channel, not at the glutamate binding site. This characteristic plus its low affinity for the channel enables memantine to discriminately block abnormal glutamate activity. Once glutamate binds to its receptor, memantine falls away. Through this mechanism of action, memantine remotely modulates the receptor, preventing excessive flow but allowing normal function. Theoretically, in the presence of this drug, abnormal glutamate activity that leads to neuronal loss is prevented, but physiological activation that produces learning and memory is preserved. Acetylcholine neurons rescued from excitotoxicity will then be available for further treatment using an acetylcholinesterase inhibitor, as described earlier. Moreover, if memantine can prevent abnormal glutamate neurotransmission, it may provide neuroprotection in both the early stages of many different neurodegenerative diseases when toxicity is generated, e.g., due to the presence of brain inflammation, as well as later in the disease process, when symptoms are more apparent. To the extent that similar mechanisms contribute to cell death in other neurodegenerative diseases, memantine could theoretically slow their progression as well (Mobius, 2003).

Alzheimer's disease is acknowledged to be a disease of multifactorial pathology expressed through a range of cognitive, behavioral, and functional symptomatology. These characteristics, together with its progressive nature, suggest that treatment with a combination of drugs may maximize response to therapy. A reasonable prediction, then, is that memantine and an acetylcholinesterase inhibitor should work together effectively to optimize pharmacotherapy for AD patients (Wenk et al., 2000a; Daiello et al., 2005; Doody et al., 2003). Recent clinical trial results support this prediction.

IX. ROLE OF OXIDATIVE STRESS AND MITOCHONDRIA FAILURE IN NEURODEGENERATION

Deficits in energy metabolism associated with aging play an important role in the vulnerability of neurons and in neurodegenerative diseases, such as AD (Beal, 1995; Blass et al., 2000; Emeritt et al., 2004). A defect in energy production would make neurons that express glutamatergic receptors more vulnerable to elevated or normal levels of endogenous glutamate for the following reasons. Decreased levels of intracellular ATP would lead to a partial, and chronic, membrane depolarization, the relief of the voltage-dependent Mg$^{2+}$ blockade at NMDA receptors, and a persistent increase in the influx of calcium ions into the cells. Ultimately, the accumulation of intracellular calcium ions following the activation of NMDA receptors by glutamate would lead to
neuronal death. Oxidative stress or impaired intracellular calcium buffering may also result in impaired energy production, possibly leading to impaired function of the membrane ion pumps required for maintenance of the resting potential. In any of these situations, excessive calcium ion influx through NMDA receptors could activate a host of calcium ion–dependent signaling pathways and stimulate nitric oxide production through closely associated neuronal nitric oxide synthase. Nitric oxide can react with a superoxide anion to form peroxynitrite, which disintegrates into extremely toxic hydroxyl free radicals that can further impair mitochondrial function and energy production. Intracellular calcium may become concentrated within the post-synaptic mitochondria, further contributing to the impaired energy production within the region of the NMDA channels (Peng and Greenamyre, 1998; Duchen, 2000).

Mitochondrial dysfunction coupled with activation of glutamatergic receptors could underlie enhanced cholinergic vulnerability associated with aging and AD. These results suggest that under conditions that lead to a mitochondrial energy deficit, such as that produced by exposure to 3-nitropropionic acid, activation of NMDA receptors can lead to the death of the neuron (Wenk et al., 1996). In addition, mitochondrial dysfunction might have a much greater and earlier impact on the integrity of cholinergic neurons, in part due to their dependence on normal mitochondrial function for the production of acetyl coenzyme A, a precursor to the synthesis of acetylcholine on normal mitochondrial function. These findings are consistent with the hypothesis that mitochondrial failure and neurochemical processes involving NMDA receptor overactivation and oxidative stress play a role in neurodegeneration in vulnerable brain regions (Barnham et al., 2004).

X. NEURODEGENERATIVE DISEASES ASSOCIATED WITH β-AMYLOID

AD is characterized by progressive deterioration of cognition and memory and disturbed emotional reactivity caused by dysfunction and degeneration of neurons in the limbic system and cerebral cortex. Affected brain areas typically contain extracellular neuritic plaques composed of fibrillar Aβ deposits and intracellular neurofibrillary tangles composed of paired helical filaments of hyperphosphorylated tau. The deposition of Aβ is a key element leading to the neuronal loss seen in the AD brain. The gradual accumulation of Aβ in the interstitial fluid of the brain may provide a focus for the subsequent deposition of other proteins and the release of inflammatory proteins by activated glia; these conditions may promote the transformation of diffuse filamentous Aβ deposits into a possibly more neurotoxic form (Schubert et al., 1998). The accumulation of toxic fibrillar Aβ in the surrounding neuropil may be a prin-
ciple stimulus for the activation of resident microglia to secrete cytokines and reactive oxygen species (Meda et al., 1999). Neuronal homeostasis may become disrupted and eventually induce cell death (Cowburn et al., 1997). Aβ also induces oxidative stress and perturbs neuronal ion homeostasis by promoting membrane lipid peroxidation, which can impair the function of membrane-bound ion, glucose, and amino acid (including glutamate) transport proteins. In addition to producing oxidative stress and affecting Ca²⁺ homeostasis, Aβ may increase the vulnerability of neurons to glutamate, leading to glutamate excitotoxicity and the opportunity for NMDA channel antagonists to reduce this vulnerability. Aβ can chronically depolarize neurons through its action on the metabotropic glutamate receptor, mGluR1 (Blanchard et al., 2002), and partially relieve the voltage-dependent Mg²⁺ blockade of NMDA channels. Under these conditions, subsequent activation of NMDA receptors by ordinary glutamatergic synaptic activity could permit a continuous entry of calcium ion into neurons, overwhelming the endogenous mechanisms that regulate calcium homeostasis. Therefore, due to the continuing presence of Aβ, neurons that express NMDA receptors would become selectively vulnerable to normal glutamatergic stimulation. This is similar to the situation described earlier due to the presence of chronic brain inflammation.

XI. β-AMYLOID: TREATMENT APPROACHES

Aβ can interact with NMDA receptors and enhance NMDA receptor-mediated excitotoxicity. For example, radioligand-binding experiments in rat cortical membranes suggest that Aβ selectively binds to the glutamate and glycine binding sites of the NMDA receptor, and not to non-NMDA glutamate receptor subtypes (Cowburn et al., 1997). Mature cultured murine cortical neurons and fetal human cerebral cortical cell cultures exposed to Aβ were more susceptible to excitotoxic injury by glutamate or NMDA as compared to neurons that were not exposed to Aβ (Kim and Ko, 1998; Mattson et al., 1992). Given the role of the NMDA channel in the vulnerability of neurons, it was not surprising that a chronic infusion of memantine reduced local neuronal cell loss produced by intrahippocampal injection of Aβ (Miguel-Hidalgo et al., 2002). Indeed, a brief exposure of cultured cortical neurons to memantine, which would produce only a transient block of NMDA receptors, inhibited the toxicity of Aβ for up to 48 hours (Tremblay et al., 2000). The relevance of this brief effect of memantine with regard to chronic therapy in AD remains to be investigated.

In transgenic mice that demonstrate an accelerated amyloid deposition in hippocampus and cortex that is associated with dystrophic neurites and reactive astrocytes (Price et al., 1998) and suppressed gene expression underlying consolidation (Dickey et al., 2004), memantine improved performance in both
T-maze and Morris water maze paradigms for spatial working memory and spatial long-term memory, respectively (Tanila et al., 2003). In cultured human neuroblastoma cells, treatment with memantine for 24–48 hours provided evidence that the drug may enhance amyloid degradation (Chen et al., 2002). It remains to be determined whether memantine can produce a similar disease-modifying effect in the AD brain. To the extent that similar mechanisms contribute to cell death in AD and age-related neurodegenerative diseases, selective NMDA channel antagonists could theoretically slow their progression as well.

In spite of the enormous amount of research effort that has focused on AD and other neurodegenerative disorders, the underlying pathophysiological processes are not understood in sufficient detail to guide the design of effective drug therapies. For example, the relationship between the presence of specific genes associated with AD and the appearance of amyloid deposits has focused attention on the molecular pathways involved in amyloid clearance and strategies to prevent amyloid production and aggregation. The current strategy is to try to reduce Aβ production from amyloid precursor protein (APP). APP is a transmembrane protein that is normally metabolized via one of two well-studied pathways associated with the enzymes α-secretase, β-secretase, or γ-secretase. APP processing via the α-secretase pathway avoids the formation of Aβ. APP processing via the sequential activities of the β- and γ-secretases leads directly to the production of the toxic form of Aβ and its subsequent deposition into senile plaques. Therapeutic strategies have been tested using these secretases as targets; for example, drugs have been produced that can lead to the stimulation of α-secretase, inhibition of β-secretase, or inhibition of the γ-secretase (Citron, 2004). Pharmaceutical companies have investigated the effects on γ-secretase inhibitors on the progression of the pathology and dementia associated with AD (Citron, 2004). Although research using these drugs on transgenic animal models of AD has produced promising results, there are significant drawbacks due to lack of substrate specificity. The problem is that the APP processing molecules would be only one of many potential substrates that could be influenced by γ-secretase inhibitors (De Strooper et al., 1999).

XII. NMDA RECEPTOR FUNCTION IN NEURODEGENERATIVE DISEASES ASSOCIATED WITH TAU PROTEINS

The evidence just discussed indicates a clear negative effect of Aβ on the function of NMDA receptors. In addition, NMDA receptor function can alter the expression and functional state of tau. Tau is a microtubule-associated protein that promotes microtubule polymerization and stabilization. Hyperphosphory-
lated tau accumulates in paired helical neurofilaments to form neurofibrillary tangles in the brains of patients with AD. A potential link between glutamate-induced excitotoxicity and tau was first demonstrated by studies using cultured rat hippocampal neurons; glutamate-induced neurodegeneration was associated with immunostaining that was specific for the presence of neurofibrillary tangles (Mattson, 1990). Acute or chronic NMDA-induced excitotoxicity in neuronal cultures can also significantly enhance tau production (Pizzi et al., 1995; Sindou et al., 1992) and selectively increases phosphorylated tau (Couratier et al., 1996, 1997). Given the potentially significant role of neurofibrillary tangle formation in the clinical progression of AD dementia (Bierer et al., 1995) and that augmented tau phosphorylation can be prevented by an NMDA receptor antagonist (Couratier et al., 1996), it is likely that NMDA receptor-dependent influences on tau phosphorylation could promote the evolution of AD pathology and dementia. The abnormal hyperphosphorylation of tau may be related to the impaired activity of protein phosphatase (PP)-2A; treatment with the NMDA antagonist memantine restored PP-2A function and reduced the accumulation of tau in a rat hippocampal slice preparation (Li et al., 2004). Taken together, these findings suggest that NMDA receptors play a critical role in the progress of neuropathology associated with tauopathies and that drugs similar to memantine might be useful for the treatment.

XIII. TREATING NEURODEGENERATIVE DISEASE SYMPTOMS WITH GINKGO BILOBA

Negative results for therapies targeting those cognitive impairments described earlier are often underrepresented in the scientific literature. This fact underscores the need for caution when assessing the cognitive enhancing or neuroprotective effects of any drug; this is particularly true for herbal medications that target the brain. Today, extracts of the Ginkgo biloba tree are perhaps the herbal treatment most widely used specifically to augment cognitive functions, particularly memory impairments associated with normal aging and neurodegenerative diseases. Ginkgo has been used by humans in different cultures for centuries and, at the very least, is a relatively safe, although likely inert, treatment. The few published studies that show an enhancement of learning and memory in rodents are difficult to evaluate due to insufficient information about experimental procedures. Close examination of the dozens of investigations of the cognitive effects of ginkgo in humans quickly leads one to conclude that the drug produces only mild beneficial effects on various aspects of cognitive functioning (Gold et al., 2003). The majority of studies have involved subjects with significant cognitive impairments, typically a diagnosis of early-to middle-stage Alzheimer’s disease, or, more recently, in healthy normal elderly subjects who are typically classified as having mild to moderate
cognitive impairment. In general, these studies have found quite limited, but sometimes statistically significant, improvements in performance on various standardized tests of cognitive function after chronic treatment with ginkgo, as compared with placebo. The improvements were usually revealed using tests requiring various cognitive abilities, such as attention, short-term memory, and choice reaction time. In healthy elderly subjects, the available data do not as yet allow any conclusion to be made with certainty. None of the potential effects of ginkgo in humans reported to date are clearly attributable to direct effects of the drug on memory processes. In each case, indirect effects of the drug on memory via effects on other cognitive processes (such as arousal and attention) are probable (Gold et al., 2003).

Ginkgo may enhance the uptake of choline into acetylcholine-releasing neurons (Kristofikova and Klaschka, 1997). Increased availability of choline might be able to enhance the production of acetylcholine within these neurons. Similar therapeutic approaches have led to the use of diets enriched with choline. The production and release of acetylcholine also requires the availability of other precursors, which can be derived from dietary glucose. Consumption of ginkgo extract can increase glucose utilization and acetylcholine production in the frontal and parietal cortex and cerebellum, areas of the brain that are important for processing sensory information and movement and for attentional abilities (Kunkel, 1993). However, the problem is that even though these neurons might synthesize and store more acetylcholine presynaptically, they do not necessarily increase their probability of release of acetylcholine. Thus, the ultimate impact of increased acetylcholine formation on cognitive performance is unclear.

A comparison of the efficacy of ginkgo with acetylcholinesterase inhibitors (Oken et al., 1998) showed that the mean extent of improvement resulting from gingko treatment was approximately 10–20%, a value roughly comparable to the magnitude of improvement often seen in clinical trials with acetylcholinesterase inhibitors. A direct comparison in rats of ginkgo versus acetylcholinesterase inhibitors showed clearly greater efficacy of the enzyme inhibitors. A recent six-week randomized, double-blind, placebo-controlled, parallel-group trial involving over 200 healthy elderly patients examined the effects of ginkgo using standardized neuropsychological tests of verbal and nonverbal learning and memory, attention and concentration, naming and expressive language abilities (Solomon et al., 2002). There were no significant benefits due to the ginkgo therapy on any outcome measure. These data suggest that when taken following the manufacturer's instructions, ginkgo provides no measurable benefit in memory or related cognitive function to adults with healthy cognitive function.

Overall, there is simply too little data to base a clear recommendation regarding the benefits of ginkgo extracts, or any other herbal or pharmaceutical agent, on learning and memory or other cognitive functions. Many years of
experience with investigations of new drugs have demonstrated that the initial positive results from studies involving a small number of subjects tend to disappear when the drugs are tested on larger numbers of subjects from diverse populations.

**XIV. TREATMENT APPROACH OF THE FUTURE: NEUROPROTECTION**

Anti-inflammatory drugs, secretase inhibitors, and NMDA antagonists offer the potential of neuroprotection against neurodegeneration involving inflammation, amyloid deposition, and glutamate excitotoxicity. Theoretically, treatments focused on these processes should slow the progression of AD. In AD, glutamatergic dysfunction, the consequences of chronic inflammation, prolonged oxidative stress, Aβ and tau production, and deposition not only contribute to the cell death but also interact with each other, leading to exaggerated pathology through positive feedback mechanisms. However, the principle problem in identifying the neuroprotective actions of these treatment approaches is related to the long treatment durations (1–3 years) that are required to demonstrate true neuroprotection from the neurodegenerative processes that are thought to underlie AD. Drug toxicity and side-effect profiles also become more important in the elderly, increasing further problems with long-term treatment. Clinical trials aimed at showing neuroprotection requires both placebo control groups and a relatively long washout period from the drug to ensure that testing is done when drug is not present in the brain. There are clear ethical concerns about such clinical trial design. That is, is it appropriate to withhold treatment to test a scientific theory? Any drug that exhibits potential neuroprotective properties will require long follow-up periods to allow beneficial effects to be clearly documented. In addition, neuroprotective trials will need to utilize drugs that target different aspects of the known neurodegenerative changes discussed earlier. The best clinical outcome may be achieved by a combination of therapies, particularly if the intent is to demonstrate synergistic effects over time. Combination drug therapies may require that the dose of each drug be reduced in order to limit the drug toxicity; unfortunately, combination therapy will likely add to the overall cost and complexity of trial design. Given our earlier discussions, a combination therapy would consist of agents targeting chronic neuroinflammation, oxidative stress, Aβ, and tau. Thus far, there have been few attempts to show neuroprotective activity in AD. Numerous epidemiological studies strongly indicate that people taking anti-inflammatory drugs have a significantly reduced prevalence of AD or a slower cognitive decline. Although interventional studies have not been successful, anti-inflammatory treatment is likely to be more effective when administered many years prior to the onset of symptomatic AD, a time when
brain inflammation is more prominent (McGeer and McGeer, 1998; Mackenzie and Munoz, 1998; Wyss-Coray and Mucke, 2000; Akiyama et al., 2000; Gahtan and Overmier, 1999; Wenk et al., 2000b).

XV. SUMMARY

This chapter has presented evidence that demonstrates that no pharmacological treatment available today has been demonstrated to slow the consequences of human aging on the decline in cognitive function associated with neurodegenerative disease. Studies of the neuropathological changes associated with specific diseases, primarily AD, have improved our understanding of the neural processes that might be targeted for manipulation; unfortunately, the initial results from clinical trials on humans have not been encouraging. Currently, if one desires to attenuate the consequences of aging and possibly slow the decline in learning and memory abilities, only one intervention, the consumption of a low-calorie, nutritionally balanced diet, can effectively increase longevity and prolong good health (Lane et al., 2002). Therefore, bon raisonnable appétit!

REFERENCES


Marchetti B and Abbracchio MP (2005) To be or not to be (inflamed) — is that the question in anti-inflammatory drug therapy of neurodegenerative diseases? *TIPS* 26: 517–525.


