Kirk-Othmer Encyclopedia of Chemical Technology.

MEMORY-ENHANCING DRUGS

Memory enhancement therapy can be viewed as generally beneficial to many individuals, not only those whose ability to function on a day to day basis has been compromised. For various reasons, however, drugs potentially useful as memory or cognition enhancers are exclusively being developed to treat patients who have been diagnosed with some form of mnemonic or cognitive impairment. Thus, potential memory-enhancing drugs are discussed herein predominantly from the standpoint of treatments that intervene in one or more processes associated with the development of dementia.

Dementia is a condition characterized by impairments in short-term memory, language, visuospatial skills, and alertness resulting from reduced intellectual functioning. Alzheimer's disease (AD) is the most prevalent form of dementia. It is the fourth leading cause of death in the United States, and as of 1990 was estimated to cost $82 billion, annually (1). AD is a neurodegenerative disease of unknown etiology leading to a primary lesion in the cerebral cortex and hippocampus. The functional deficits resulting from the loss of cortical neurons are exacerbated by the loss of several subcortical neuronal systems that project to the cerebral cortex. The systems include the cholinergic, dopaminergic, serotonergic, and noradrenergic. These subcortical afferents play an important role in regulating cortical excitability and resulting cortical function. The degradation and eventual breakdown of the functional connectivity within the cerebral cortex lead to the cognitive impairments seen in AD. Whereas AD is associated with the severest forms of compromised cognitive function and memory, some loss of these functions is generally present in later life even for AD-free individuals and is accepted as a condition known as age-associated memory-impairment (AAMI). In many cases, the causes of AD and AAMI may be similar, such that only the degree of affliction serves as the differentiating factor. Thus efficacious therapies in the severest form of this affliction may also be beneficial in the milder ones.

As of this writing (ca 1994) no drugs are available to address the etiology of neuronal loss and consequent memory impairment. There are, however, a number of drugs used throughout the world that enhance cerebral metabolism or that palliate cognitive dysfunction through modulation of neurotransmitter systems. Whereas there is considerable controversy surrounding the clinical efficacy of these agents, cognition enhancers are sold worldwide and comprise an annual market estimated to be between $1 and $2 billion (2). Widespread usage results largely from availability and the absence of alternative therapy. The hope is that these agents can provide some benefit to patients, no matter how small the probability of efficacy or magnitude of effect.

The compounds used to palliate the mnemonic and cognitive decline associated with dementia include cerebral vasodilators and the so-called nootropic agents. These materials enhance cerebral metabolism. Agents which enhance neurotransmitter function are in most cases cholinergic.

1. Cerebral Metabolism Enhancers

Whereas the majority of agents being evaluated for treatment of dementia have activities associated with specific neuronal systems, cerebral metabolism enhancers have undefined or varied mechanisms. Hydergine (**1**)vinpocetine [42971-09-5] (**2**), and nimodipine [66085-59-4] (**3**) initially had been thought to exert their

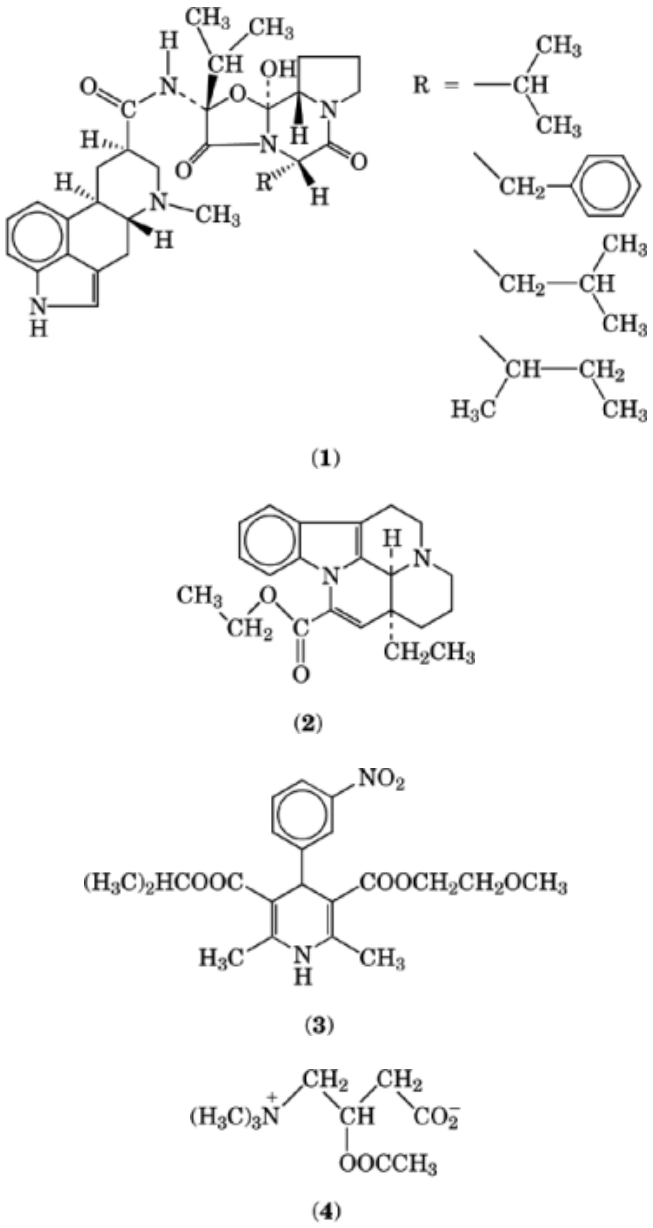


Fig. 1. Structures of cerebral metabolism enhancers.

activity through cerebral vasodilation (Fig. 1). However, these are used to treat patients with dementia or other age-related symptoms of compromised cognitive function based on other mechanisms and without a clear understanding of the reasons for beneficial actions. The other agent in this group, acetyl-L-carnitine [14992-62-2] (**4**) is thought to exert its beneficial effects by its positive influence on energy metabolism in the mitochondria, as well as on cholinergic activity.

Hydergine (Du Pont), also referred to as ergoloid mesylates (**1**), is a combination of four dehydrogenated derivatives of the ergot alkaloid ergotoxine [8006-25-5] (see Alkaloids). Usage is restricted to treatment of patients with compromised cognitive functions. There is only limited clinical evidence to support its efficacy (3). The effects in patients with possible AD have been modest at best. Moreover, benefits have been associated with behavioral rather than cognitive measures. Beneficial effects appear to be stronger in a subgroup having vascular dementia than in a subgroup having possible AD.

The primary evidence for the cerebral metabolic-enhancing activity of Hydergine is its ability to improve brain oxygen consumption (P_{O2}) and electrical activity reduced by oligemic hypovolemia, a reduction in blood circulation (4). Hydergine has been reported to increase neuronal noradrenaline release, but the drug itself acts to block these effects at the post-synaptic $_1$-adrenoceptors. In addition, Hydergine has partial agonist activity at dopaminergic and serotonergic systems (5). More recently it has also been shown by microdialysis techniques that Hydergine enhances the release of acetylcholine in the hippocampus in a dose-dependent manner (6). This is a response similar to both dopamine D_1 and D_2 receptor antagonists. These latter properties may in part explain the behavioral changes observed in AD patients that have been treated with the drug. Because of the history of poor efficacy in AD, the U.S. Food and Drug Administration (FDA) had been pressured to remove Hydergine from the market.

Vinpocetine (**2**), another drug initially categorized as a cerebral vasodilator, is a member of the vinca alkaloid family of agents (7). However, interest in this compound as a potential drug for learning and memory deficits comes from its ability to act as a neuronal protectant. This compound was evaluated in 15 patients with AD over a one-year period and was ineffective in improving cognitive deficits or slowing the rate of decline (8). However, in studies of patients with chronic vascular senile cerebral dysfunction (9) and organic psychosyndrome (10), vinpocetine showed beneficial results.

The neuroprotective properties of vinpocetine may be related to its anticonvulsant properties (11). It has been suggested that convulsions (*status epilepticus*) cause neuronal loss by excessive intracellular calcium produced by neuronal burst firing (12). This firing is believed to be caused by an excessive stimulation of *N*-methyl-D-aspartic acid (NMDA) [6384-92-5] glutamate receptors leading to calcium influx and cell loss. This process may be common to convulsions, cerebral ischemia, and neurodegenerative disorders (13). Compounds such as vinpocetine that have the ability to inhibit ischemia-induced neuronal death (14) may also have a neuronal protectant effect in diseases like AD and AAMI rather than immediately improving the symptoms.

Consistent with the ability of vinpocetine to act as an anticonvulsant is its ability to inhibit cellular reuptake of adenosine (15) which has been described as the brain's endogenous anticonvulsant because of its ability to inhibit calcium influx. Thus the property of vinpocetine to inhibit adenosine reuptake may be responsible for the neuroprotective actions of the drug.

In addition, vinpocetine selectively inhibits a specific calcium, calmodulin-dependent cyclic nucleotide phosphodiesterase (PDE) isozyme (16). As a result of this inhibition, cyclic guanosine 5′-monophosphate (GMP) levels increase. Relaxation of smooth muscle seems to be dependent on the activation of cyclic GMP-dependent protein kinase (17), thus this property may account for the vasodilator activity of vinpocetine. A review of the pharmacology of vinpocetine is available (18).

Nimodipine (**3**), a member of the dihydropyridine series of calcium channel blockers, has been shown to cause cerebral vessel dilation and increase cerebral blood flow in animals and humans (19–21). This drug decreases the severity of neurological deficits and reduces mortality and morbidity of patients with subarachnoid hemorrhage, an indication for which it is marketed in the United States (22). The ability of this agent to reduce the frequency of vasospasm was initially thought to be the basis of its pharmacological action. This has not been demonstrated, however, either angiographically or by noninvasive cerebral blood flow studies. These observations suggest that nimodipine may increase microcirculatory or collateral blood flow to underperfused regions, or provide a direct neuronal protective effect.

The interest in nimodipine for the treatment of individuals with compromised cognitive function is based, in part, on suggestions that blocking neuronal calcium channels may be an effective treatment for

memory impairments associated with brain injury as well as age-related memory failure (23). Clinical studies have attempted to demonstrate the benefit of the highly lipophilic, and thus blood brain barrier penetrating nimodipine in a randomized, double-blind, placebo-controlled, multicenter study of 227 AD patients. The drug-treated group was reported to experience a prophylactic benefit across eight measures when contrasted with disease progression seen among placebo recipients (24). Nimodipine also improved clinical symptomatology and cognitive functions in patients having primary degenerative dementia (25). The patients with multiinfarct dementia were less favorably affected. The divergent therapeutic responses of these groups suggest that the protection of neuronal tissue from calcium overload rather than cerebral vasodilatation may be the reason for the neuroprotective effects of the agent.

The death of cholinergic cell bodies originating in the nucleus basalis of Mynert is a principal neuropathological find in AD. A pharmacological strategy to slow the rate of cholinergic neuronal death should be protective and thus effective in the treatment of AD (26). Because increases in cytosolic free calcium triggers the neuronal death mechanisms, agents that inhibit this rise through calcium channel blockade may prove to retard the progress of this disease. Moreover, even in the normal aging process, changes in cellular calcium regulation may be disrupted (27). Because nimodipine has been shown to reduce neuronal degeneration in a variety of toxic conditions, and increase neuronal firing of aged neurons in addition to its cerebrovascular effect, this drug appears to have promise for patients with compromised age-related mental deficits.

Acetyl-L-carnitine (**4**) is marketed in Italy for dementia; as of this writing it is also in Phase III clinical trials in the United States and Europe. In a double-blind, placebo-controlled clinical trial over a one-year period involving 130 patients with clinically diagnosed AD, a slower rate of deterioration in 13 of the 14 outcome measures was observed in the drug-treated group (28). Earlier smaller scale pilot studies in demented patients had also shown some improvement of various behavioral and cognitive functions (29).

Acetyl-L-carnitine is an endogenous substance involved in the uptake of activated long-chain fatty acids into mitochondria. Studies in rats have also shown that this compound increases acetyl-coenzyme A (acetyl-CoA) and choline acetyltransferase activities, choline uptake, and acetylcholine release (30), supporting earlier studies that demonstrated the central cholinergic effects of the drugs (31). Thus a beneficial effect of the drug on cognitive function may be associated with its positive influence on energy metabolism in the mitochondria and on cholinergic activity. The pharmacology of this agent in the central nervous system (CNS) has been reviewed (32).

More recently, acetyl-L-carnitine has been shown to enhance the response of rat PC12 cells to nerve growth factor (NGF) stimulating the synthesis of NGF receptors (33). This agent may rescue aged neurons by increasing their responsiveness to neurotrophic factors in the CNS. In rats having impairment of cholinergic activity resulting from transection of the fimbria fornix, 150 mg/(kg·d) acetyl-L-carnitine was found to increase the level of NGF as well as choline acetyltransferase, an index of cholinergic processes, in the septum and frontal cortex (34). These data are suggestive of a neurotrophic property exerted by the drug on those central cholinergic pathways typically damaged by aging. Agents like acetyl-L-carnitine that mimic the trophism exerted by NGF have been proposed as therapeutic treatments for AD (35).

2. Nootropics

The term nootropic has been used to describe a class of compounds defined by the ability of its members to facilitate learning (36). The compounds are most effective in animals that have had their cognitive abilities compromised in some way. The molecular mechanism underlying the cognitive-enhancing effects of this class of molecules is unknown, although interaction with the excitatory amino acid network (37–39), muscarinic M-1 receptors (40, 41), or enzymes such as prolylendopeptidase (42) have been suggested. Piracetam [7491-74-9] (**5**) is the classic representative of the group and many other acetams, such as aniracetam [72432-10-1] (**6**), oxiracetam [62613-82-5] (**7**), pramiracetam [68497-12-1] (**8**), nebracetam (**9**), and nefiracetam (**10**) are

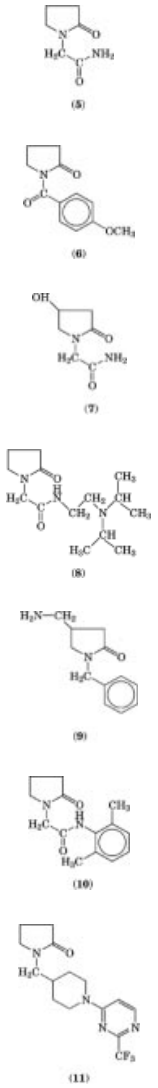


Fig. 2. Structures of nootropic agents.

undergoing or have undergone clinical evaluation. At least 18 different nootropic agents, including certain cerebral vasodilators, are being evaluated worldwide by various companies. The nootropics are the largest class of compounds being considered for patients with AD or compromised memory and cognition function. Structures are shown in Figure 2.

The mechanism of action of nootropic agents has been proposed to be their ability to facilitate information acquisition, consolidation, and retrieval (36). No one particular effect has been observed with any consistency for these agents, thus whereas a considerable amount of diverse preclinical pharmacological behavioral data has been generated using these compounds, the significance of these results in predicting clinical efficacy has

not been established (43, 44). Reviews on the biochemical and behavioral effects of nootropics are available (45–47).

Piracetam (**5**) and related analogues facilitate selected aspects of learning and memory as indicated in a variety of animal studies (43, 45, 48). Human studies, however, have not been as definitive (43, 49). There has been indication of efficacy in patients with mild to moderate dementia (50) as well as in AD patients (51), but the results are not compelling. Piracetam's mechanism of action has been related to effects on cholinergic neurotransmission (46), binding to glutamate receptors (52), activation of brain adenylate cyclase (53), increases in cerebral glucose utilization (54), and potentiated increase in adenosine 5′-monophosphate (AMP)-induced calcium influx (37). However, demonstration of these effects often occurs at concentrations or dosages much higher than the serum or brain levels of drug achieved in humans. Thus the lack of definitive cognitive-enhancing action using piracetam may result from the inability to achieve sufficient plasma concentrations of drug to trigger or sustain these types of responses. In spite of this questionable efficacy, piracetam has been marketed in 85 countries beginning in 1973. In addition to use for the symptomatic treatment of AD, it is also indicated for cerebro-vascular injury or insufficiency, ie, specific learning disabilities such as dyslexia, alcoholism, and vertigo. A comprehensive review on the biochemical, pharmacological, and pharmacokinetic properties and clinical effectiveness of piracetam and structurally related nootropics has been published (55).

Oxiracetam (**7**) is the 4-hydroxy derivative of piracetam. This agent was initially launched in Italy in 1987 and although it has not produced convincing results in AD patients (56, 57), beneficial effects have been reported in patients with multiinfarct dementia after chronic use (57–59). Various studies suggest that the action of oxiracetam may involve NMDA receptors (60). An indirect mechanism is likely. Like piracetam, oxiracetam increases the density of specific binding sites for *dl*,α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) in synaptic membranes from rat cortex, and does not act on metabotropic glutamate receptors (37). In addition, oxiracetam stimulates choline uptake into isolated hippocampal slices from spontaneously hypertensive rats having sodium chloride-induced cerebrovascular lesions (61). The drug also enhances K^+-induced acetylcholine release from rat hippocampal slices and stimulates choline acetyltransferase (CAT) (62). Each or all of these actions may contribute to the nootropic effect of oxiracetam. However, a review has described the potential therapeutic effects in the context of the influence of endogenous steroid levels, and proposes that these hormones should be considered well in advance of nootropic therapy (47).

Aniracetam (**6**), launched in 1993 in both Japan and Italy for the treatment of cognition disorders, is in Phase II trials in the United States as of this writing. In clinical studies it has been shown to cause some improvement in elderly patients with mild to moderate mental deterioration (63), and in geriatric patients with cerebral insufficiency (64). In a multicenter double-blind placebo-controlled trial involving 109 patients with probable AD, positive effects were observed in 36% of patients after six months of treatment (65), a result repeated in a separate study of 115 patients (66). A review of the biological and pharmacokinetic properties, and clinical results of aniracetam treatment in cognitively impaired individuals is available (49).

Electrophysiological studies indicate that aniracetam prolongs the time course and increases the peak amplitude of the fast excitatory post-synaptic currents (EPSCs) and strongly reduces glutamate receptor desensitization (67, 68). Other actions include recruitment of a subset of AMPA-sensitive glutamate receptors which normally do not contribute to synaptic transmission, as suggested for oxiracetam (37). A large number of *in vivo* pharmacological studies have demonstrated that aniracetam also influences cholinergic neurotransmission. In addition, effects on the dopaminergic, adrenergic, and serotonergic systems have also been observed (55). Aniracetam inhibits prolylendopeptidase (PEP), an enzyme associated with the degradation of endogenous proline-containing neuropeptides, that may have beneficial actions on memory and learning (69). The multifacted pharmacological profile of this agent makes it an intriguing prospect, although the therapeutic utility is still undergoing evaluation.

Pramiracetam (**8**), a piracetam derivative having a dialkylaminoalkyl group on the acetamide nitrogen, was launched in Italy in 1993 for the treatment of attention and memory deficits resulting from degenerative or vascular disorders. Whereas the drug was reported to show some benefit in male patients with memory and

cognitive problems resulting from head trauma (70), it was without benefit in AD patients (44). More recently, in a multicenter open trial involving 104 elderly patients with cognitive or memory impairment of probable vascular origin, pramiracetam showed better efficacy in patients with moderate compared to those with mild impairment (71).

Unlike aniracetam, pramiracetam does not appear to interact with dopaminergic, serotonergic, or adrenergic neurotransmission (72). The agent inhibits prolylendopeptidase in certain brain areas, but its inhibition constant, K_i, is only 11 μM (69). The absence or weak activity of this compound with various neuronal systems appears to make it less likely to be of significant therapeutic value than other members of this class of agents.

Other nootropic agents in some stage of clinical development include nebracetam (**9**), nefiracetam (**10**), and BMY 21502 (**11**). Nebracetam, an aminomethyl pyrrolidinone derivative, is expected to be approved in Japan in 1994 (73). In clinical studies involving patients having cerebrovascular or senile dementia of the Alzheimer's type, clinical symptoms such as spontaneous or emotional expression were enhanced in up to 71% of cases. Long-term treatment using nebracetam in patients with cerebral infarction also afforded marked improvement in most cases with few side effects (74). A review of this compound has been published (75).

Unlike the other pyrrolidinone nootropic agents, various studies support a cholinergic mechanism of action for nebracetam. In rat brain membranes, nebracetam (**9**) possesses affinity for cholinergic receptors (40). The agent also has direct actions on nicotinic and muscarinic acetylcholine receptors expressed in Xenopus oocytes (76). The impaired working memory and learning acquisition induced in rats by AF64A, a neurotoxic choline analogue, were ameliorated by the drug (77). Nebracetam has also been shown to reverse scopolamine- and AF64A-induced memory impairments in rats (77–79). In addition, studies also support the involvement of limbic and hippocampal noradrenergic mechanisms in the cognition-enhancing effects of the drug (79).

Nefiracetam (**10**) has been reported to show beneficial clinical results apparently arising from effects on neurochemical processes involving GABA and acetylcholine (80–83). A variety of *in vivo* pharmacological studies demonstrating the effect of nefiracetam on various types of chemically or physically induced amnesia have been reported (55, 84). Whereas many of these studies are associated with the GABAergic system, the results are difficult to interpret because of the uncertainty about GABA and the memory process (85). Other studies have demonstrated an involvement with acetylcholine neurotransmission, and nefiracetam also causes an increase in choline uptake in rat cortex (86). However, there appears to be some uncertainty regarding significant beneficial effects of nefiracetam on patients with compromised cognitive function compared to other acetams.

Limited clinical data on BMY 21502 (**11**) suggest that some benefit may be provided to patients with dementia (87, 88). This expectation is based on the ability of (**11**) to increase the level of arousal and attention in patients with certain types of dementia. BMY 21502 enhances long-term potentiation (LTP) in hippocampal slices (89, 90). LTP is believed to be a critical step in memory acquisition, and agents that possess the ability to augment this process *in vivo* are expected to be of benefit in memory enhancement. However, this compound has only demonstrated this property *in vitro*. In addition, because (**11**) does not appear to affect other neurotransmitter systems, as do other nootropics, the potential of BMY 21502 as a memory-enhancing agent is questionable.

There appear to be a number of clinical studies that support the efficacy of various nootropic agents in patients with some form or degree of dementia, but the results are not particularly convincing (50, 51, 57–59, 63, 74).

3. Cholinomimetics

One of the earliest identified and most consistent neurochemical changes observed in AD is the profound loss of neocortical cholinergic innervation (91–94). This loss correlates with the degree of dementia. Experiments in animals have also pointed to the importance of cholinergic function to learning and memory (95–97). These

observations have led to what has been called the cholinergic hypothesis of AD (98) which suggests that the cholinergic losses observed in AD lead directly to the observed cognitive and mnemonic deficits.

The wide range of neurochemical alterations documented in AD (99–101) indicates that the cholinergic hypothesis is an oversimplification. Furthermore, studies of animals having excitotoxin lesions of the basal forebrain cholinergic cell group suggest that the cholinergic projection from these cells is not as important to learning and memory as was first thought (102). This projection may, in fact, be more important to attention than to learning and memory (103). However, the role of cholinergic dysfunction in memory impairment and symptoms of dementia is well supported, although this represents only one factor of this disease.

Although controversy exists over the cholinergic involvement in AD dementia, as of 1993 the only AD therapy approved by the U.S. FDA was the cholinesterase inhibitor, tacrine [321-64-2], $C_{13}H_{14}N_2$, sold as Cognex (Warner-Lambert).

Several cholinergic strategies, other than cholinesterase inhibition, have been employed with the intention of ameliorating the symptoms of AD. These include precursor loading acetylcholine release enhancement, and direct activation of both muscarinic and nicotinic receptors.

3.1. Acetylcholine Precursors

Early efforts to treat dementia using cholinomimetics focused on choline [62-49-7] (**12**) supplement therapy (Fig. 3). This therapy, analogous to L-dopa [59-92-7] therapy for Parkinson's disease, is based on the hypothesis that increasing the levels of choline in the brain bolsters acetylcholine (ACh) synthesis and thereby reverses deficits in cholinergic function. In addition, because choline is a precursor of phosphatidylcholine as well as ACh, its supplementation may be neuroprotective in conditions of choline deficit (104).

Precursor loading using choline (qv) or lecithin (qv) (**13**) failed to have a significant effect on AD symptoms (98, 105–107). These negative results may, in part, be related to the observation that lecithin does not alter central cholinergic activity in AD (108).

α-Glycerylphosphorylcholine (α-GFC) (**14**) and cytidine-5-diphosphate-choline (CDP-choline)(**15**) are two more recently studied choline-delivering agents. The former has been reported to increase ACh production and release, and to reverse scopolamine-induced behavioral deficits in rats (109) as well as to reverse behavioral deficits in old and excitotoxin-lesioned rats (110). The latter has been shown to be effective in improving behavioral performance in compromised animals (111). α-GFC has been reported to have positive effects in treating patients with multiinfarct dementia (112, 113), and CDP-choline has been reported to be effective in treating patients with vascular dementia (112) and AD (114). However, clinical trials assessing the effects of α-GFC and CDP-choline on dementia did not employ double-blind designs.

3.2. Acetylcholinesterase Inhibitors

The greatest activity in the area of cholinomimetic treatments for AD has been in the development of agents that retard the degradation of acetylcholine (ACh) through the blockade of acetylcholinesterase (AChE) activity. Acetylcholinesterase inhibitors (AChEI) are generally effective in increasing performance in rodent models of learning and memory, especially those in which cholinergic deficits are created (115). The first AChE inhibitor to be tested in dementia, physostigmine [57-47-6] (**16**), was potent, but its efficacy was limited because of a short half-life. This limitation has been addressed in the design of newer generation compounds. Specificity of AChE inhibitors has also been a problem because many AChE inhibitors also are potent inhibitors of plasma butyrylcholinesterase, an activity which might contribute, in part, to several of the side effects associated with this class of molecules. However, the most recent compounds under investigation are relatively specific for brain AChE. Structures of AChEI are shown in Figure 4.

Physostigmine (**16**), an alkaloid, has been the most extensively studied AChE inhibitor. Through its reactive carbamoyl group, (**16**) acylates the catalytic site of AChE, thereby inhibiting the enzyme. This acylation,

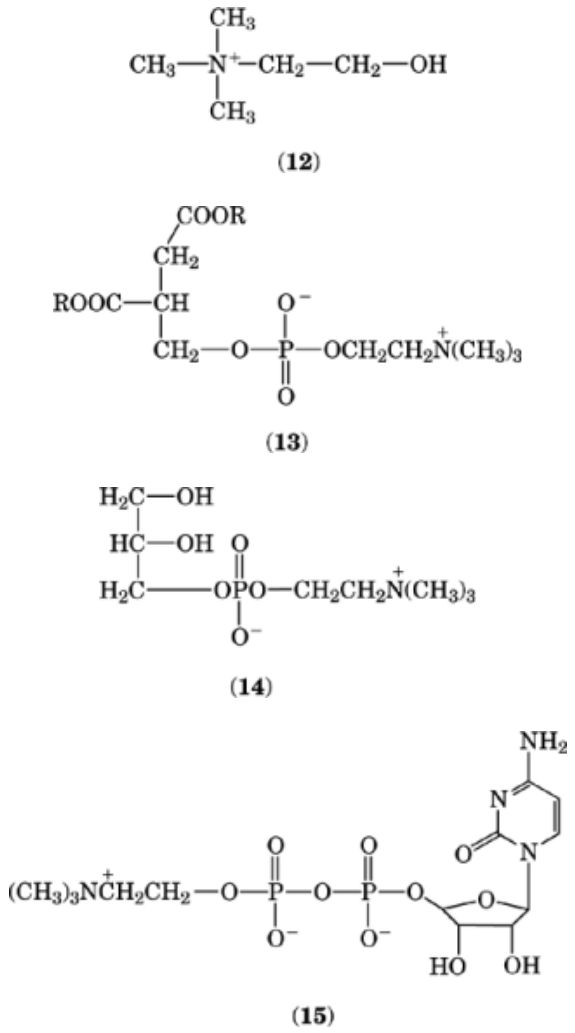


Fig. 3. Structures of acetylcholine precursors.

however, is readily reversible and physostigmine is considered a reversible inhibitor of the enzyme (116). Clinical studies demonstrated that oral physostigmine led to small cognitive improvements in a subpopulation of AD patients (116), but a narrow therapeutic window was observed. Side effects of physostigmine included gastrointestinal disturbances as well as cardiovascular effects. Other shortcomings of physostigmine are a short half-life and variable bioavailability (117).

Heptylphysostigmine (eptastigmine) (**17**) has been shown to be as active as physostigmine in AChE inhibition, but superior to physostigmine in terms of oral bioavailability and half-life (118–120). However, further clinical evaluation of this compound has been halted because of drug-related hematological toxicity.

SDZ ENA 713 (**18**) is another long-acting carbamate-containing molecule being investigated for AChE inhibition and AD therapy. The advantage claimed for this compound over physostigmine, heptylphysostigmine, and tacrine (**19**) is the CNS specificity of SDZ ENA 713 relative to the other AChE inhibitors (121). This

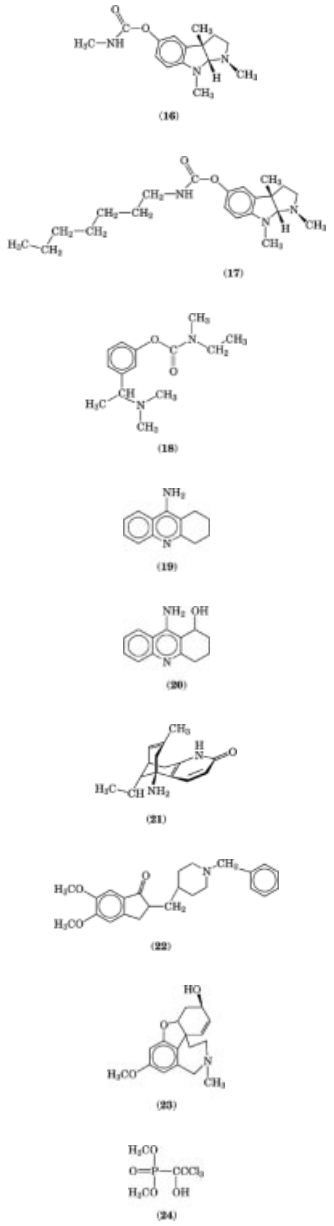


Fig. 4. Structures of acetylcholinesterase inhibitors.

selectivity may serve to reduce peripheral side effects while maintaining clinical efficacy. Central activity of SDZ ENA 713 has been observed in normal human subjects in the absence of peripheral side effects.

The aminoacridines, tacrine (**19**) and its 1-hydroxy metabolite, velnacrine (**20**), are reversible inhibitors of AChE. Tacrine was synthesized in the 1940s and has been used clinically for the treatment of myasthenia gravis and tardive dyskinesia (115). Placebo-controlled studies have indicated modest efficacy of tacrine to

treat AD dementia (122, 123) and in 1993 the drug was recommended for approval by the FDA under the trade name Cognex. Tacrine (**19**) has been shown to interact with sites other than AChE, such as potassium channels (124) and muscarinic receptors. However, these interactions are comparatively weak and are not thought to contribute to the biological activity of the drug at therapeutic levels (115).

Serious hepatotoxicity of tacrine has been documented. More recent data suggest, however, that this toxicity can be reduced by carefully monitoring serum alanine aminotransferase levels (125). The side effects of tacrine also include gastrointestinal disturbances and emesis, and alternative AChE therapies are being advanced. Velnacrine (**20**), a metabolite of tacrine, was expected to have reduced hepatotoxicity. However, its limited efficacy and side-effect profile, which includes drug-related hematological changes, caused it to be dropped from further development.

Three structurally unrelated AChE inhibitors being pursued for AD treatment are huperzine A (**21**), E2020 (**22**), and galanthamine [357-70-0] (**23**). Huperzine A is an alkaloid extracted from the Chinese herb *Huperzia serrata*. It is an effective treatment for myasthenia gravis (126) and has been suggested as an effective treatment for aged individuals with memory impairment (127). The drug has a long duration of action (128) and a favorable side-effect profile (129). At the present time the compound is being tested in broader clinical trials.

E2020 (**22**) is a relatively specific brain acetylcholinesterase inhibitor. It is over 500 times more selective for AChE than for butyrylcholinesterase (130). In addition, E2020 inhibits brain cholinesterase in a dose-dependent manner without a significant effect on enzyme activity in the intestine or heart. E2020 has an extremely long elimination half-life of about 60 h in young subjects and 104 h in elderly individuals (131). The specificity of this compound may provide a much better safety profile than other AChE inhibitors. The long half-life of the compound may complicate dosing, however.

Galanthamine (**23**) is an alkaloid extracted from the common snowdrop *Galanthus nivalis*. This compound is a long-acting, competitive AChE inhibitor which appears to be somewhat more specific for acetylcholinesterase than plasma butyrylcholinesterase (132). It is well tolerated during long-term treatment (133) and is being evaluated clinically for AD (134).

Metrifonate [52-68-6] (**24**) is itself not an AChE inhibitor, but is nonezymatically converted into an active irreversible inhibitor of the enzyme. The compound is relatively specific for AChE over butyrylcholinesterase (135) and the irreversible nature of its inhibition gives rise to an extended duration of action. Some clinical experience has been gained through its use to treat schistosomiasis (136, 137) and it is undergoing clinical evaluation for AD.

4. Receptor Agonists

4.1. Muscarinic Receptor Agonists

Acetylcholine indirect agonists such as the AChE inhibitors and ACh-releasing agents only have value in treating dementia if enough of the cholinergic arbor in the hippocampus and cortex of affected individuals remains functional. As the cholinergic innervation declines, as is the case upon progression of AD, these therapies lose efficacy. However, there is evidence that post-synaptic receptors actually are preserved in AD (138, 139). Thus direct muscarinic agonists should remain effective even as the presynaptic cholinergic terminals decline in number.

Initial attempts to treat AD using direct cholinergic agonists were limited by low efficacy and side-effect issues (140–142). Thus trials using RS-86 (**25**), oxotremorine [70-22-4] (**26**), arecoline [63-75-2] (**27**), and pilocarpine [92-32-7] (**28**) to treat AD were equivocal (Fig. 5). However, the identification of multiple subtypes of muscarinic receptors has stimulated a search for subtype specific muscarinic agonists which may limit side effects while increasing efficacy.

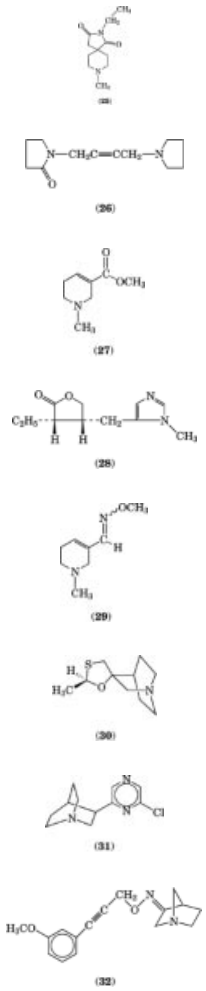


Fig. 5. Structures of muscarinic agonists.

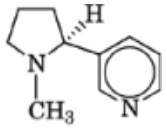
Five distinct muscarinic receptors have been identified (143) designated m1 to m5. The m1 receptor is believed to be important for increasing cerebral cortical tone, and therefore may be an important target for AD therapy (144). The m2 receptor, on the other hand, is thought to be associated with cholinergic side effects such as emesis and bradycardia. It has been determined that many of the first muscarinic agonists evaluated were more potent for m2 receptors. More recently, however, balanced m1/m2 receptor agonists, as well as m1 selective agonists, have been or are being tested.

CI-979 (**29**) is a balanced muscarinic agonist having equal affinities for cloned m1 and m2 receptors (144). However, unlike prototypical muscarinic compounds such as (**25**), (**29**) increases central muscarinic tone, as indicated by behavioral and electroencephalogram (EEG) parameters, at doses lower than those required to produce gastrointestinal effects (144). CI-979 is well tolerated in humans up to a dose of 1 mg. Dose-limiting side effects such as stomach pain and emesis were observed at a dose of 2 mg.

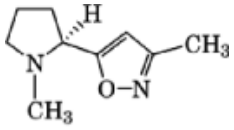
Whereas balanced muscarinic agents having acceptable therapeutic indexes may be of clinical value, more hope is held for subtype specific agents. AF-102b (**30**) and L-689,660 (**31**) appear to be low efficacy muscarinic drugs that display a functional specificity for m1 and m3 receptors (145). These compounds act as antagonists at m2 receptors (145). AF-102b has similar affinity for both m1 and m2 receptors, and its specificity is based on its functional activity at these receptors (144). Unlike AF102b, PD 142505 (**32**) has a threefold higher affinity for m1 over m2 receptors (144). PD 142505 has been shown to enhance performance in a spatial working memory task in mice at doses of 1 and 3.2 mg/kg po. Moreover, the compound does not cause increases in gastrointestinal motility at doses as high as 178 mg/kg in the rat (144).

4.2. Nicotinic Receptor Agonists

There has been significant activity in the development of muscarinic cholinergic receptor agonists for dementia. In addition, agents that interact with nicotinic cholinergic receptors may also have therapeutic value. Nicotinic receptors have been reported to be reduced in AD, and pilot clinical data on the use of nicotine [54-11-5] **(33)** in AD have suggested some benefit of the drug (146). However, the gastrointestinal and cardiovascular side effects of nicotine limit its therapeutic value. Thus efforts to discover brain specific nicotinic agonists for AD treatment led to ABT 418 **(34)**. This compound was shown to be 3–10 times more potent than nicotine in enhancing performance of laboratory animals in paradigms designed to measure learning and memory. In contrast, ABT 418 was less potent than nicotine in producing emesis (147). ABT 418 is being evaluated in human clinical trials.



(33)



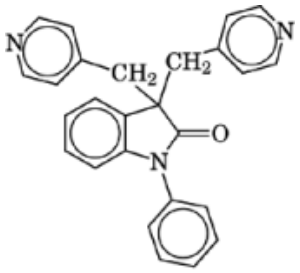
(34)

5. Acetylcholine Release Modulators

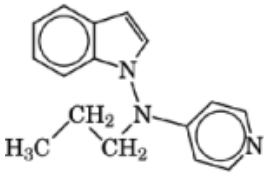
An alternative approach to stimulate cholinergic function is to enhance the release of acetylcholine (ACh). Compounds such as the aminopyridines increase the release of neurotransmitters (148). The mechanism by which these compounds modulate the release of acetylcholine is likely the blockade of potassium channels. However, these agents increase both basal (release in the absence of a stimulus) and stimulus-evoked release (148). 4-Aminopyridine [504-24-5] was evaluated in a pilot study for its effects in AD and found to be mildly effective (149).

Unlike the aminopyridines, linopirdine **(35)** (AVIVA) enhances evoked and not basal release of acetylcholine (150). In rats, linopirdine has been shown to enhance the acquisition response and reverse the passive avoidance deficits elicited by hypoxia (151, 152). Like 4-aminopyridine, **(35)** enhances the release of several neurotransmitters. Linopirdine has been shown to enhance the K^+-stimulated release of [^{3}H]acetylcholine from neocortical, hippocampal, and striatal slices, as well as the K^+-stimulated release of [^{3}H]dopamine and

[^{3}H]serotonin from striatal slices without affecting the basal efflux of these neurotransmitters (150). In contrast, the drug has no effect on the release of [^{3}H]norepinephrine from rat neocortical slices (150). Because the functions of multiple neurotransmitter systems are decreased in dementias like AD, the property of compounds such as linopirdine to enhance the release of several neurotransmitters offers an advantage over AD therapies aimed at stimulating the cholinergic system alone.



(35)



(36)

Another compound that affects parameters relating to several neurotransmitter systems is HP749 **(36)** which is in clinical trials for the treatment of the dementia associated with Alzheimer's disease. In passive avoidance paradigms, **(36)** was found to be active in reversing scopolamine-induced amnesia in mice, and enhancing retention in normal and nucleus basalis lesioned rats (153). This compound has several effects in *in vitro* neurochemical assays including monoamine reuptake blockade, enhancement of NE release, and inhibition of α_2-adrenergic and muscarinic receptor binding.

Age-related syndromes of cognitive and memory decline ultimately may be treated by agents that slow or stop the progression of dementia, but available therapy as of this writing offers only symptomatic relief. Of the many approaches to palliative treatment for dementia that have been attempted, the greatest effort has been in the areas of cerebral metabolism (cerebral vasodilators and nootropics) and neurotransmission (primarily cholinergic) enhancers. Only the acetylcholinesterase inhibitor tacrine is accepted as having therapeutic effect in a subpopulation of those suffering with AD dementia.

BIBLIOGRAPHY

"Memory-Enhancing Agents and Antiaging Drugs" in *ECT* 3rd ed., Vol. 15, pp. 132–143, by J. S. Bindra, Pfizer, Inc.

Cited Publications

1. Robertson, *Inter. J. Health Serv.* **20**, 429 (1990).
2. *Current Drugs: Neurodegenerative Disorders,* NDG4 (1994).
3. L. S. Schneider and J. T. Olin, *Arch. Neurol.* **51**, 787 (1994).

4. N. Meyer-Rouge and co-workers, *Pharmacology* **16**, 45 (1978).
5. R. Markstein, *J. Pharmacol* **16**, 1 (1985).
6. A. Imperato and co-workers, *Neuro Report* **5**, 674 (1994).
7. T. Imamoto, M. Tanabe, N. Shimamoto, K. Kawazoe, and M. Hirata, *Arzneimittelforschung* **34**, 161 (1984).
8. L. J. Thal, D. P. Salmon, B. Lasler, D. Bower, and M. R. Klanber, *J. Am. Geriatr. Soc.* **37**, 515 (1989).
9. R. Balestreri and R. Fontana, *J. Am. Geriatr. Soc.* **35**, 425 (1987).
10. L. Blaha, H. Erizgkeit, A. Adamczyk, S. Freytag, and R. Schaltenbrand, *Human Psychopharmacol.* **4**, 103 (1989).
11. K. L. Keim and P. C. Hall, *Drug. Dev. Rev.* **11**, 107 (1987).
12. B. S. Meldrum, in I. F. C. Rose, ed., *Metabolic Disorders of the Nervous System*, Pitman, London, 1983, 175–187.
13. W. F. Margos, T. Greenamyre, J. B. Penney, and A. B. Young, *Trends Neurosci.* **10**, 65 (1987).
14. J.-C. Lamar, M. Beaughard, C. Bromont, and H. Poignet, in I. J. Kriegelstein, ed., *Pharmacology of Cerebral Ischemia*, Elsevier, Amsterdam, the Netherlands, 1986, 334–339.
15. B. B. Fredholm, E. Lindgren, L. Lindstrom, and L. Vernet, *Acta. Pharmacol. Toxicol.* **52**, 236 (1983).
16. T. Hagiwara, T. Endo, and H. Hidaka, *Biochem. Pharmacol.* **33**, 453 (1984).
17. S. H. Francis, B. D. Noblett, B. W. Todd, J. N. Wells, and J. D. Corbin, *Mol. Pharmacol.* **34**, 506 (1988).
18. C. D. Nicholson, *Psychopharmacology* **101**, 147 (1990).
19. A. Scriabine, T. Schuurman, and J. Traber, *FASEB J.* **3**, 1799 (1989).
20. M. S. Langley and E. M. Sorkin, *Drugs* **37**, 669 (1989).
21. A. N. Wadworth and D. McTavish, *Drugs Aging* **2**, 262 (1992).
22. F. B. Meyer, *Neurosurg. Clin. N. Am.* **1**, 367 (1990).
23. M. Sandin, S. Jasmin, and T. E. Levere, *Neurobiolog. Aging* **11**, 573 (1990).
24. G. D. Tollefson, *Biol. Psychiatry* **27**, 1133 (1990).
25. P. K. Fischhof, *Methods Find Exp. Clin. Pharmacol.* **15**, 549 (1993).
26. R. J. Branconnier, M. E. Branconnier, T. M. Walshe, C. McCarthy, and P. A. Morse, *Psychopharmacol. Bull.* **28**, 175 (1992).
27. M. C. deJonge and J. Traber, *Clin. Neuropharm.* **16**, 525 (1993).
28. A. Spanoli and co-workers, *Neurology* **41**, 1726 (1991).
29. D. Cucinotta and co-workers, *Drug Dev. Res.* **14**, 213 (1988).
30. A. Imperato, M. T. Ramacci, and L. Angelucci, *Neurosci. Lett.* **107**, 25 (1989).
31. M. Onofri, I. Bodis-Wollner, P. Pola, and M. Calvani, *Drugs Exp. Clin. Res.* **9**, 161 (1983).
32. L. Janiri and E. Tempesta, *Int. J. Clin. Pharmacol. Res.* **3**, 295 (1983).
33. G. Taglialatela and co-workers, *Dev. Brain Res.* **59**, 221 (1991).
34. P. Piovesan, L. Pacifics, G. Taglialatela, M. T. Ramacci, and L. Angelucci, *Brain Res.* **633**, 77 (1994).
35. C. H. Phelps and co-workers, *Neurobiol. Aging* **10**, 205 (1989).
36. C. Giurgea, *Drug. Dev. Res.* **2**, 441 (1982).
37. A. Copani and co-workers, *J. Neurochem* **58**, 1199 (1992).
38. L. J. Vyklicky, D. K. Patneau, and M. L. Mayer, *Neuron.* **7**, 971 (1991).
39. S. Ozawa, M. Iino, and M. Abe, *Neurosci. Res.* **12**, 72 (1991).
40. Y. Kitamura, S. Hayashi, and Y. Nomura, *Jpn. J. Pharmacol.* **52**, 597 (1990).
41. Y. Kitamura, T. Kaneda, and Y. Nomura, *Jpn. J. Pharmacol.* **55**, 177 (1991).
42. T. Yashimoto and co-workers, *J. Pharmacobio-Dyn.* **10**, 730 (1987).
43. M. W. Vernon and E. M. Sorkin, *Drugs Aging* **1**, 17 (1991).
44. J. J. Calus and co-workers, *Neurology* **41**, 570 (1991).
45. E. Gamzu, T. Hoover, S. Gracon, and M. Ninteman, *Drugs Dev. Res.* **18**, 177 (1989).
46. G. Pepeu and G. Spignoli, *Prog. Neuro-Psychopharmacol. Biol. Psych.* **13**, 577 (1989).
47. C. Mondadori, *Behavioral Brain Res.* **59**, 1 (1993).
48. U. Schindler, *Prog. Neurosychopharmacol. Biol. Psych.* **13**, (Suppl.), 99 (1989).
49. X. Rabasseda, N. Mealy, and N. Presti, *Drugs Today* **30**, 9 (1994).
50. W. M. Hermann and K. Stephan, *Alzheimer Dis. Assoc. Disorder* **5**(Suppl. 1), 7 (1991).
51. M. A. Passeri, *Symposium on Piracetam: 5 Years' Progress in Pharmacology and Clinics,* Tenicas Grarficas Formas, Madrid, 1990, p. 75.
52. B. Bering and W. E. Müller, *Arzneim.-Forsch./Drug Res.* **35**, 1350 (1985).

53. V. J. Nicholson and O. L. Wolthuis, *Biochem, Pharmacol.* **25**, 2241 (1976).
54. M. Grau, J. L. Monter, and J. Balasch, *Gen. Pharmacol.* **18**, 205 (1987).
55. A. H. Gouliaev and A. Senning, *Brain Res. Revs.* **19**, 180 (1994).
56. A. Falsaperla, P. A. Monici-Petri, and C. Oliani, *Clin. Ther.* **12**, 376 (1990).
57. L. Parnetti and co-workers, *Neuropsycholpharmacology* **22**, 97 (1989).
58. B. Baumel and co-workers, *Prog. Neuropsychopharmacol. Biol. Psych.* **13**, 673 (1989).
59. G. Maina and co-workers, *Neuropsychobiology* **21**, 141 (1989).
60. M. Marchi, E. Basana, and M. Raiteri, *Eur. J. Pharmacol.* **185**, 247 (1990).
61. C. Nardella and co-workers, *Farmaco* **46**, 1051 (1991).
62. D. Mochizuki, G. Sugiyama, Y. Shinoda, *Nippon Yagurigaku Zasshi* **99**, 27 (1992).
63. V. Canonico and co-workers, *Riv. Neurol.* **61**, 92 (1991).
64. G. Forloni, N. Angeretti, D. Amorsoso, A. Addis, and S. Consolo, *Brain Res.* **530**, 156 (1990).
65. U. Senin and co-workers, *Neurophyschopharmacology* **1**, 511 (1991).
66. L. Parnetti and co-workers, *Dementia* **2**, 262 (1991).
67. C. M. Tang, O. Y. Shi, A. Katchman, and G. Lynch, *Science* **254**, 288 (1991).
68. J. S. Isaacson and R. A. Nicoll, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 10936 (1991).
69. T. Yashimoto and co-workers, *Pharmacobio-Dyn.* **10**, 730 (1987).
70. A. McLean, D. D. Cardenas, D. Burgess, and E. Gamzu, *Brain Inj.* **5**, 375 (1991).
71. P. Scarpazza and co-workers, *Adv. Ther.* **10**, 217 (1993).
72. T. A. Pugsley, Y. H. Shih, L. Coughenour, and S. F. Stewart, *Drug Dev. Res.* **3**, 402 (1983).
73. *Scrip* **20**, 1833 (1993).
74. T. Kinoshita and co-workers, *Jpn. Pharmacol. Ther.* **19**, 179 (1991).
75. *Drugs Future* **18**, 18 (1993).
76. H. Aoshima, R. Shingai, and T. Ban, *Arzneim-Forsch-Drug Res.* **42**, 775 (1992).
77. M. Hashimoto, T. Hashimoto, and T. Kuriyama, *Eur. J. Pharmacol.* **209**, 9 (1991).
78. M. Ohno, T. Yamamoto, I. Kitajima, and S. Ueki, *Jpn. J. Pharmacol* **54**, 53 (1990).
79. K. Iwasaki, Y. Matsumoto, and M. Fujiwara, *Jpn. J. Pharmacol.* **58**, 117 (1992).
80. T. Nabeshima, *Neuropsychopharmacology* **9** (Suppl.), 110 (1993).
81. M. Yoshii, S. Watabe, *Brain Res.* **642**, 123 (1994).
82. S. Watanabe, H. Yamaguchi, and H. Ashida, *Jpn. J. Pharmacol.* **52** (Suppl. 1), 294P (1990).
83. S. Watanabe, H. Yamaguchi, and H. Ashida, *Eur. J. Pharmacol.* **238**, 303 (1993).
84. M. Tanaka, K. Takasuna, and S. Takayama, *Arzneim.-Forsch./Drug Res.* **44**, 193 (1994).
85. M. Sarter, *Trends. Pharm. Sci.* **12**, 456 (1991).
86. S. Watanabe, H. Yamaguchi, and S. Ashida, *Neurosci. Abstr.* **15**, 601 (1989).
87. A. Berardi and co-workers, *Neurosci. Abst.* **17**, 698 (1991).
88. A. Berardi and co-workers, *J. Neurosci. Abstr.* **18**, 1243 (1992).
89. V. K. Gribkoff, L. A. Bauman, and C. P. Vandermaelen, *Soc. Neurosci Abst.* **14**, 207 (1988).
90. V. K. Gribkoff, L. A. Bauman, and C. P. Vandermaelen, *Neuropharmacology* **20**, 1001 (1990).
91. P. Davies and A. J. F. Maloney, *Lancet* **11**, 1403 (1976).
92. E. K. Perry and co-workers, *Br. Med. J.* **2**, 1427 (1978).
93. P. Whitehouse and co-workers, *Science* **215**, 237 (1982).
94. J. T. Coyle, D. Price, and M. DeLong, *Science* **219**, 1184 (1983).
95. S. R. El-Defrawy and co-workers, *Neurobiol Aging* **6**, 325 (1985).
96. M. Watson, T. W. Vickroy, H. C. Fibiger, W. R. Roeske, and H. I. Yamamura, *Brain Res.* **346**, 387 (1985).
97. D. J. Hepler, G. L. Wenk, B. L. Cribbs, D. S. Olton, and J. T. Coyle, *Brain Res.* **346**, 8 (1985).
98. R. T. Bartus, R. L. Dean, B. Beer, and A. S. Lippa, *Science* **217**, 408 (1982).
99. D. L. Price, *Ann Rev Neurosci.* **9**, 489 (1986).
100. R. J. D'Amato and co-workers, *Ann. Neurol.* **22**, 229 (1987).
101. R. G. Struble and co-workers, *J. Neuropathol Exp. Neurol.* **46**, 567 (1987).
102. S. B. Dunnett and H. C. Fibiger, in A. C. Cuello, ed., *Cholinergic Function and Dysfunction*, Vol. **98**, Elsevier Science Publishers BV, Amsterdam, the Netherlands, 1993, p. 413.
103. M. L. Voytko and co-workers, *J. Neurosci.* **14**, 167 (1994).

104. R. J. Wurtman, *TINS* **15**, 117 (1992).
105. L. J. Thal, W. Rosen, N. S. Sharpless, and H. Crystal, *Neurobiol. Aging* **2**, 205 (1981).
106. A. Little, R. Levy, K. P. Chuaqui, and D. Hand, *J. Neurol. Neurosurg. Psychiatry* **48**, 736 (1985).
107. A. Heymen and co-workers, *J. Neural Transm. Suppl.* **24**, 279 (1987).
108. N. Pomara and co-workers, *J. Clin. Psychiatry* **44**, 293 (1983).
109. C. M. Lopez and co-workers, *Pharmacol. Biochem. Behav.* **39**, 835 (1991).
110. F. Drago and co-workers, *Pharmacol. Biochem. Behav.* **41**, 445 (1992).
111. F. Drago and co-workers, *Brain Res. Bull.* **31**, 485 (1993).
112. P. R. Di and co-workers, *J. Internat. Med. Res.* **19**, 330 (1991).
113. S. G. Barbagallo, M. Barbagallo, M. Giordano, M. Meli, and R. Panzarasa, *Annal. N.Y. Acad. Sci.* **717**, 253 (1994).
114. J. Caamano, M. J. Gomez, A. Franco, and R. Cacabelos, *Meth. Findings Exp. Clin. Pharmacol.* **16**, 211 (1994).
115. J. C. Jaen and R. E. Davis, *Neurodegenerative Disorders*, 87–101 (1993).
116. L. J. Thal, in R. Becker and E. Giacobini, eds., *Physostigmine in Alzheimer's Disease*, Birkhauser, Boston, Mass., 1991.
117. L. J. Thal, P. A. Fuld, D. M. Masur, and N. S. Sharpless, *Ann. Neurol.* **13**, 491 (1983).
118. L. L. Iversen and co-workers, in R. Becker and E. Giacobini, eds., *Cholinergic Basis for Alzheimer Therapy*, Birkhauser, Boston, Mass., 1991, p. 297.
119. P. DeSarno, M. Pomponi, E. Giacobini, X. C. Tang, and E. Williams, *Neurochem. Res.* **14**, 971 (1989).
120. E. Messamore, U. Warpman, N. Ogane, and E. Giacobini, *Neuropharmacology* **32**, 745 (1993).
121. A. Enz, R. Amstutz, H. Boddeke, G. Gmelin, and J. Malanowski, *Prog. Brain Res.* **98**, 431 (1993).
122. M. Farlow and co-workers, *JAMA* **268**, 2523 (1992).
123. K. L. Davis and co-workers, *New Eng. J. Med.* **327**, 1253 (1992).
124. S. E. Freeman and R. M. Dawson, *Prog. Neurobiol.* **36**, 257 (1991).
125. P. B. Watkins, H. J. Zimmerman, M. J. Knapp, S. I. Gracon, and K. W. Lewis, *JAMA* **271**, 992 (1994).
126. Y. Cheng and co-workers, *New Drugs Clin. Rem.* **5**, 197 (1986).
127. S. Zhang, *New Drugs Clin. Rem.* **5**, 260 (1986).
128. X. C. Tang, P. DeSarno, K. Sugaya, and E. Giacobini, *J. Neurosci. Res.* **24**, 276 (1989).
129. X. F. Yan, W. H. Lu, W. J. Lou, and C. Tang, *Acta Pharamacol. Sin.* **8**, 117 (1987).
130. S. Araki, Y. Yamanishi, T. Kosasa, H. Oguru, and K. Yamatsu, *Jpn. J. Pharmacol.* **49** (Suppl.), (1989).
131. A. Ohnishi and co-workers, *J. Clin. Pharmacol.* **33**, 1086 (1993).
132. T. Thomsen and H. Kewitz, *Life Sci.* **46**, 1553 (1990).
133. T. Thomsen, U. Bickel, J. P. Fischer, and H. Kewitz, *Dementia* **1**, 46 (1990).
134. P. Dal-Bianco and co-workers, *J. Neural. Trans.* **33** (Suppl.), 59 (1991).
135. R. E. Becker, P. Moriearty, and L. Unni, in Ref. 118, p. 263.
136. P. R. Mason, S. A. Tswana, P. Jenks, and C. E. Priddy, *J. Tropical Med. Hygiene* **94**, 180 (1991).
137. A. F. Mgeni and co-workers, *Bull. World Health Org.* **68**, 721 (1990).
138. D. Mash, D. Flynn, and L. Potter, *Science* **228**, 1115 (1985).
139. B. Pearce and L. T. Potter, *Alz. Dis. Assoc. Disord.* **5**, 163 (1991).
140. M. M. Mouradian, E. Mohr, J. A. Williams, and T. N. Chase, *Neurology* **38**, 606 (1988).
141. K. L. Davis and co-workers, *Am. J. Psychiatry* **144**, 468 (1987).
142. S. L. Read and co-workers, *Arch. Neurol.* **47**, 1025 (1990).
143. T. L. Bonner, N. J. Buckley, A. C. Young, and M. R. Brann, *Science* **237**, 527 (1987).
144. R. Davis and co-workers, *Prog. Brain Res.* **98**, 439 (1993).
145. L. L. Iversen, in Ref. 102, 423–426.
146. P. A. Newhouse and co-workers, *Psychopharmacol. Berlin* **95**, 171 (1988).
147. M. W. Decker and co-workers, *J. Pharmacol. Experimen. Therap.* **270**, 319 (1994).
148. R. L. Buyukuysal and R. J. Wurtman, *J. Nuerochem.* **54**, 1302 (1990).
149. H. Wesseling and co-workers, *N. Engl. J. Med.* **310**, 988 (1984).
150. V. J. Nickolson, S. W. Tam, M. J. Meyers, and L. Cook, *Drug Dev. Res.* **19**, 285 (1990).
151. N. V. Cook, L. Steinfels, K. W. Rohrbach, and V. J. DeNoble, *Drug Devel. Res.* **19**, 301 (1990).

152. V. J. DeNoble and co-workers, *Pharmacol. Biochem. Behav.* **36**, 957 (1990).
153. M. Cornfeldt and co-workers, *Soc. Neurosci. Abstr.* **20**, 252.6 (1990).

ROBERT ZACZEK
The Du Pont Merck Research Laboratories
ROBERT J. CHORVAT
The Du Pont Merck Research Laboratories

Related Articles

Alkaloids