Nicotinic Treatment of Alzheimer’s Disease

Paul A. Newhouse, Alexandra Potter, Megan Kelton, and June Corwin

Approximately 20 years after the formulation of the “cholinergic hypothesis” to explain the cognitive symptoms of Alzheimer’s disease, cholinesterase therapy remains the mainstay of treatment for this disorder. Although partially effective, currently available agents have limited effects on cognitive function and long-term efficacy appears modest. Direct or indirect stimulation of nicotinic cholinergic receptors may offer an additional therapeutic strategy. Ongoing investigations of the molecular substructure of central nervous system nicotinic receptors, their accompanying pharmacology, and the effects of nicotinic agents on cognitive function have suggested the possibility that nicotinic stimulation may have beneficial effects in Alzheimer’s disease and other neuropsychiatric disorders. Studies from our laboratory and others have explored the role of central nervous system nicotinic mechanisms in normal human cognitive and behavioral functioning as well as their role in Alzheimer’s disease. Results from acute therapeutic trials with nicotine and novel nicotinic agents suggest that nicotinic stimulation in Alzheimer’s disease patients can improve the acquisition and retention of verbal and visual information and decrease errors in cognitive tasks, as well as improve accuracy and response time. Whether such results will translate into improved clinical functioning remains to be fully tested. Development of subtype-selective nicotinic agonists with an improved safety profile will enable long-term testing of the efficacy of nicotinic stimulation on cognitive performance as well as potential cytoprotective effects. Direct or indirect (allosteric) modulation of nicotinic receptor function offers a new opportunity for Alzheimer’s disease therapeutics. Biol Psychiatry 2001;49:268–278 © 2001 Society of Biological Psychiatry

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Introduction

The underlying cause(s) of Alzheimer’s disease (AD) appear to be disruption of the regulation, expression, or scavenging of abnormal membrane-associated proteins (e.g., β-amyloid leading to neurotoxicity). This neurotoxicity leads to a degeneration of a variety of neurotransmitter systems that presumably are responsible for the clinical and cognitive manifestations of the illness. Although a myriad of neurochemical deficits have been described in AD, explanation of the nature of the cognitive disturbances has been most closely focused on the “cholinergic hypothesis,” which implicates disturbances in central muscarinic cholinergic mechanisms in normal cognitive functioning and disorders of memory function (Bartus et al 1982; Drachman and Leavitt 1974).

Nicotinic mechanisms may be important in explaining the pathophysiology and in designing treatments for AD (James and Nordberg 1995). Patients suffering from AD have a marked reduction in cortical nicotinic cholinergic receptor binding relative to age-matched control subjects (Aubert et al 1992; Flynn and Mash 1986; Whitehouse et al 1986). Normal aged subjects show an age-related decline in cortical nicotinic binding (Flynn and Mash 1986). Warman and Nordberg (1995) used the nicotinic agonists epibatidine and ABT-418 to show selective losses of α4β2 nicotinic receptors in the brains of patients with AD. Perry et al (1995) showed that the entorhinal cortex (important in memory formation), rich in nicotinic binding, appears particularly vulnerable to amyloid plaque–induced loss of receptors. More generally, Perry and colleagues (Perry et al 1995) have shown that nicotine receptor loss seems tightly linked to the primary pathology in the dementias (e.g., linked to dopaminergic cell loss in Parkinson’s disease [PD] and Lewy Body dementia) and linked to amyloid plaques and tangles in hippocampal and parahippocampal areas in AD.

Neuroimaging studies also support the involvement of nicotinic cholinergic systems in AD. Nordberg (1993) showed a significant correlation change between the change in temporal cortex labeling of [11C]nicotine and cognitive function scores in AD patients using positron emission tomography (PET). This result was bolstered by further work from these investigators (Nordberg et al 1995) in which a kinetic model was developed to quantify...
the loss of nicotinic receptor binding in vivo in AD patients. Significant correlations were shown between cognitive dysfunction and the loss of nicotinic receptor binding in temporal and frontal cortices and the hippocampus in these patients using PET. Nordberg (1993) also examined the effects of treatment with the anticholinesterase tacrine on AD patients using PET and showed that brain nicotinic receptor binding of [11 C]nicotine increased along with cerebral blood flow after 3 weeks of treatment.

Interest in the possibility of utilizing agents that directly interact with nicotinic receptors for the treatment of central nervous system (CNS) disease has followed as understanding of the structure, function, and distribution of CNS nicotinic receptors has increased. Ongoing investigations of the molecular substructure of CNS nicotinic receptors and their pharmacology have begun to open up new possibilities for novel CNS therapies with nicotinic agents (Arneric et al 1995). There is considerable evidence from both animal and human studies for the involvement of CNS nicotinic cholinergic receptors in a variety of cognitive, motor, and behavioral systems. Modulation of these receptors with the ultimate goal of producing therapeutic benefits is the goal of these investigations and drug development.

Research in this laboratory has focused over a number of years on studies designed to understand more fully the role of central nicotinic systems in normal and disordered human cognition, particularly degenerative neuropsychiatric conditions such as AD and PD. Furthermore, we have conducted pilot studies of nicotinic drugs as “proof of concept” studies to assist in the design of longer term clinical trials of potential nicotinic agents. We briefly review those studies here and interpret them in the light of renewed interest in nicotinic mechanisms in AD and PD and the potential for meaningful nicotinic modulation of cognitive and behavioral functioning.

**Nicotinic Antagonist Studies**

Studies utilizing antagonists are useful for establishing the cognitive relevance of neuroreceptor changes in the brain as they produce a temporary chemical “lesion.” Newhouse and colleagues (Newhouse et al 1992, 1993, 1994) have studied the effects of the centrally active noncompetitive nicotinic antagonist and peripheral ganglionic blocker mecamylamine on cognitive functioning in young (n = 12, mean age 24) and elderly (n = 15, mean age 63) normal subjects and patients with mild to moderate AD (n = 11, Global Deterioration Scale = 3–5) and PD (n = 11, Hoehn-Yahr stages 1–2) disease. These studies showed that nicotinic blockade produced cognitive impairment in humans and that there were age-and disease-related changes in sensitivity to nicotinic blockade, indicated by shifts in dose–response curves between groups. Mecamylamine administration produced dose-related impairment of the acquisition of new information with group differences in sensitivity. Young normal subjects showed significant cognitive impairment after the highest dose. By contrast, the elderly normal subjects showed significant impairment after the middle and high doses, and the AD subjects showed impairment after all three active doses.

The Repeated Acquisition Task, a nonverbal serial learning task, was used to show the effects of nicotinic blockade. Subjects are asked to learn a series of button pushes on a specialized keyboard with feedback provided only by the computer. As feedback is only provided by the computer and initial choices are random, it is possible to examine the shape of the learning curve and maintenance of learning over time. Furthermore, as a sequence of button pushes (chain) is taught before the drug administration begins, it is possible to examine both well-learned information (previously learned chain) and new learning that takes place after drug administration (new chain). In addition, the task is easily adapted to populations with different learning capacities simply by changing the length of the chain.

Mecamylamine produces errors in the acquisition phase of this task. Examination of individual curves shows that mecamylamine impaired both the acquisition of new information and the ability to hold that information in working memory. Figure 1 demonstrates that, as subjects become older and/or demented, the sensitivity to the error-producing effects of mecamylamine increases, demonstrated by a shift in the dose–response curve to the left. However, results from the “performance” phase of this task (not shown) demonstrate no dose-related impairment, suggesting that nicotinic blockade does not affect the retrieval of well-learned information.

Negative effects of nicotinic blockade can also be seen in the acquisition of new verbal information using the Selective Reminding Task. Although there were no significant effects in young normal volunteers, mecamylamine produced a significant increase in recall failure at the highest dose of mecamylamine tested (20 mg) in elderly volunteers and impairment at all active doses in patients with AD. In the AD patients, the learning rate (amount of information learned or acquired divided by the amount of information remaining to be learned) actually became negative at 10 and 20 mg of mecamylamine (Figure 2), suggesting that subjects were forgetting recently learned information faster than they were acquiring new information.

In addition, mecamylamine produced a dose-related slowing of reaction time and liberalization of response bias in recognition memory tasks. This latter effect is particularly interesting, given that response bias measures
are abnormal in AD. Response bias is a mathematical expression of decision-making criteria under conditions of uncertainty. Liberal response bias tends to be characteristic of AD patients and may be clinically manifest in the overinclusiveness and nonselectivity of AD patients’ memory performance (Snodgrass and Corwin 1988). These results suggest that the deficits produced by mecamylamine resemble in several respects those seen in AD. Deficits in short- and long-term memory, impaired attention, liberal response bias, and decreases in reaction time are hallmarks of the dementing picture seen in these disorders. The age- and disease-related nature of some of the findings supports the hypothesis that increasing sensitivity is related to the increasing loss of nicotinic receptors.

Although a full comparison is beyond the scope of this review, there are similarities and differences between the effects of the nicotinic antagonist mecamylamine and muscarinic antagonists, such as scopolamine or atropine, on cognitive function. Mecamylamine generally produces qualitatively similar though quantitatively smaller effects on acquisition of new information—for example, in the Repeated Acquisition Task (Higgins et al 1989) or verbal learning (Newhouse et al 1988; Sunderland et al 1989). The combination of muscarinic and nicotinic blockade produces additive effects, particularly on explicit memory performance (Little et al 1998). Mecamylamine does not generally produce significant effects on arousal, as is commonly seen with muscarinic antagonists (Robbins et al 1997), and effects on behavior are minimal relative to the effects of scopolamine (Newhouse et al 1994).

### Nicotinic Agonist Effects

We have previously examined the effects of intravenous nicotine on cognitive, behavioral, and physiologic functioning in both normal nonsmokers and patients with AD (Newhouse et al 1988, 1993, 1996). After pilot studies aimed at establishing tolerable doses of intravenous nicotine for nonsmokers, we administered a series of intravenous doses over 60 min to a small group of patients with mild to moderate AD. The major cognitive effect seen was a significant dose-related reduction in intrusion errors on a serial learning free-recall task (Figure 3). Examination of the results shows a clear “U”-shaped dose–response curve with maximal improvement at 0.25 μg/kg/min of nicotine base.
When subjects were retested for recall of the initial word set 8 hours after the drug infusion was completed, information that was initially recalled under the conditions of the 0.25-μg dose was significantly better retained (Figure 4), suggesting a memory consolidation effect of nicotine.

Neuroendocrine measures show that nicotine induced secretion of adrenocorticotropic hormone and cortisol in a dose-related manner (Newhouse et al 1990) and tended to confirm that the doses used were active at CNS nicotinic receptors. In a later study we examined the effects of intravenous nicotine in AD with particular attention to tasks that are affected by mecamylamine (Newhouse et al 1996). Nicotine produced improvements in attentionally driven tasks, with improved reaction time, hits, and false alarms on a continuous performance task. Throughput (speed–accuracy product) was improved as well.

These findings of the beneficial results of acute nicotinic stimulation in AD have been supported by the studies of Sahakian and colleagues (Jones et al 1992; Sahakian and Coull 1994), who have shown that subcutaneous nicotine administration in AD patients produced improvements in attentional functioning. More chronic administration of nicotine to AD patients has also shown promise. Wilson and colleagues (Willson et al 1995) administered nicotine by patch to six AD patients for 8 days. Relative to the placebo patch condition, there were significantly fewer errors on the Repeated Acquisition Task while subjects were on nicotine. This effect persisted for at least a week after withdrawal. White and Levin (1999) studied 4 weeks of nicotine administration by transdermal patch in eight subjects with mild to moderate AD. The dose of nicotine varied from 5 to 10 mg/day across a 4-week period. Although no significant effects were seen on clinical measures, significant cognitive effects occurred, with improved performance on the Continuous Performance Test with reduced errors (particularly errors of omission) and reduced Reaction Time variance. A composite attention measure combining speed and accuracy showed improvement over the course of nicotine administration, suggesting an increase in throughput or work performed per unit time. However, Snaedal and colleagues (Snaedal et al 1996) were unable to find a significant effect of 4 weeks of transdermal nicotine administration on memory in 18 AD patients, possibly due to a significant placebo effect, as patients on both nicotine and a placebo showed improvements in short-term memory.

The occurrence of side effects at higher doses, such as anxiety, adverse mood changes, and nausea/vomiting, and the steepness of the dose–response confirmed animal data suggesting that, although there was evidence for therapeutic potential for nicotine in AD, the therapeutic index of nicotine itself is small and the risk of adverse side effects is significant, at least for intravenous administration. This and other work led to a search for more selective nicotinic agonists that would have a better therapeutic index, improved pharmacokinetics, and higher degree of efficacy in AD patients. ABT-418 (Abbott Laboratories, Abbott Park, IL) was the first novel selective nicotinic agonist tested in human patients. Potter and colleagues (Potter et al 1999) studied six patients with early to moderate AD in a within-subjects, repeated-measures placebo-controlled design to examine acute effects of this novel agent on cognitive functioning.

Subjects were administered doses of 6, 12, and 23 mg via a transdermal device for 6 hours. When tested at the 6-hour time point, subjects showed significant linear dose-related improvements in verbal learning and memory on the Selective Reminding Task as reflected by improved total recall and a decline in recall failure. When the change in recall and recall failure on this task was examined across the 6-hour testing period, it could be seen that ABT-418 maintained or improved performance across the day in a dose-related way relative to placebo treatment, which allowed deterioration (Figure 5). This improvement was quantitatively similar to that seen in previous acute trials with anticholinesterase inhibitors. Qualitatively similar, though not statistically significant improvements were seen in nonverbal learning tasks such as spatial learning and memory and repeated acquisition. Positive dose-related effects (speeding) on reaction time were also seen. Interestingly, subjects also showed a decline in anxiety and fear self-ratings at the 23-mg dose, consistent with prior animal studies suggesting that this agent may also have anxiolytic effects (Brioni et al 1994). No adverse behavioral, vital sign, or physical side effects were seen. These positive results echo studies of this agent in aged monkeys by Buccafusco and colleagues (Buccafusco et al 1996).
1995), who showed dose-related improvements in a delayed matching-to-sample task performance following administration of ABT-418.

Preclinical studies of other novel nicotinic agonists also show promise. Aged rats show improved learning when treated with the $\alpha_7$ selective agent GTS-21 (Taiho Pharmaceutical, Tokyo) (Arendash et al 1995). SIB-1553A (Merck, Whitehouse Station, NJ) is an $\alpha_4\beta_2$ subtype-selective nicotinic agonist and appears to be efficacious in acute and chronically stimulating hippocampal acetylcholine release (Lloyd et al 1998). This compound appears to produce enhanced performance in a variety of models of cognitive dysfunction (e.g., aged rats, rhesus monkeys, rats with cholinergic lesions) in areas such as spatial and nonspatial working and reference memory (Lloyd et al 1998). A profile such as this suggests that this compound may have activity in disorders of cortical and subcortical cholinergic dysfunction such as AD. RJR-2403 (Targacept, Winston-Salem, NC) appears to be a highly selective ligand for the $\alpha_4\beta_2$ subtype of nicotinic receptor and is the initial compound in a series of metanicotine analogs to be explored for the treatment of degenerative neuropsychiatric disorders (Lipiello et al 1996). Selective nicotinic agonists may show a greater therapeutic index than nicotine itself, although they are unlikely to be totally free of nicotinelike adverse effects such as dizziness and nausea. Such side effects were reported in a clinical trial of ABT-418 in adult attention-deficit/hyperactivity disorder patients (Wilens et al 1998) and in trials of the novel nicotinic agonist SIB-1508Y for PD (McClure 1999).

Discussion

These studies represent significant evidence that stimulation of nicotinic receptors can improve the acquisition and retention of verbal (declarative) and nonverbal information in humans. Previously, it has been difficult to demonstrate that stimulation of nicotinic receptors produces true learning or memory improvement in effects in normal subjects (Heishman et al 1994). The role of attentional effects of nicotinic stimulation has been stressed by Sahakian and Coull (1994). However, as has been suggested by Warburton and Rusted (1993), nicotine’s effects are most often seen in tasks that have a large attentional load. For example, the verbal learning tasks that showed improvement in the AD patients after acute administration of ABT-418 required focused attention and significant cognitive effort. Two recent studies by Mancuso and colleagues (Mancuso et al 1999a, 1999b) have clarified the effects of nicotinic stimulation on attentional processes. In a study of the effects of nicotinic stimulation on rapid visual information processing, a relatively low dose of nicotine was shown to improve vigilance processing in young abstinent smokers, and the effect appeared to be concentration independent (Mancuso et al 1999a). In a second study (Mancuso et al 1999b), the investigators observed that nicotinic stimulation enhances the speed of processing and number generation. There were no effects on interference performance or attentional switching. The authors interpreted these findings as consistent with the possibility that nicotinic stimulation improves the intensity feature of attention rather than affecting the selectivity of attentional processes. In essence, this appears to suggest that stimulation of nicotinic cholinergic neurons provides more attentional resources in a nonspecific way rather than improving the ability of the attentional system to select information. This can also be interpreted as providing more processing resources, which may be of additional benefit to the cognitively impaired patient. Although it appears that nicotinic modulation can improve performance on tasks that require focused attention (either verbal or spatial) and are speed dependent, nicotinic...
modulation may not improve performance on tasks that require access to semantic memory, retrieval of well-learned information, or switching between sources of information (e.g., between working memory domains).

It also may be the case that any cognitive-enhancing effects of nicotinic stimulation are more clearly manifest in cognitively impaired individuals. Nicotinic stimulation appears to show significant baseline dependency—that is, cognitive and performance effects appear to be determined in part by the baseline state of the individual (Perkins 1999). Therefore, subjects operating at a low level of performance will likely have their performance enhanced by nicotinic stimulation, whereas subjects operating at normal or above normal levels may have their performance diminished. This may help to explain why it has been difficult to demonstrate that nicotinic stimulation produces improvement in normal individuals except under conditions of deprivation. Conversely, it may be predicted that nicotinic stimulation may improve the performance of cognitively impaired individuals.

The studies reviewed here as an aggregate argue for the relevance of nicotinic receptor function in normal human cognition, motor, and possibly behavioral functioning as well as their role in disease states such as AD and PD. Though there are limitations to these studies (small sample size, wide variability in the effects of the principle agonist nicotine), they support further research into more fully elucidating nicotinic receptors’ physiologic roles. Data from these and other studies regarding the effects of nicotinic stimulation and blockade allow a preliminary synthesis regarding the role(s) of these receptor systems in normal and disordered human cognitive functioning. The loss of or alterations to nicotinic receptors and/or their associated processes may be responsible for some of the cognitive changes and blood flow alterations that are seen in AD and other neuropsychiatric disorders. Nicotinic systems appear important to normal learning and memory, but effects may be in part mediated through effects on certain aspects of attentional functioning. Effects of nicotinic receptor activation may be mediated through presynaptic regulation of catecholaminergic, cholinergic, γ-aminobutyric acid (GABA)-ergic, and/or glutamatergic transmitter mechanisms in widespread projections to the prefrontal and/or parietal cortices and basal ganglia—thalamic–prefrontal loops. What subtypes of nicotinic receptors might mediate these effects is as yet unclear, although α4β2 appears to have the greatest relevancy to AD and other cognitive disorders. The role of the α7 receptor is less clear in AD, but stimulating this receptor may be of value as well, particularly for sensory processing and/or cytoprotection.

Data suggest that nicotinic systems and/or receptors are modulatory of the release of acetylcholine, dopamine, norepinephrine, GABA, and other neurotransmitters onto their receptors. Therefore, there are probably limits to the actions of this system, and the loss of these receptors may result in the loss of a degree of control of cognitive processes rather than the underlying basic cognitive function itself. Certain cognitive processes affected in AD may not be under nicotinic modulation or influence. It appears more likely that nicotinic systems act to modulate or control the “front end” of memorial processing (e.g., control and partitioning of attentional resources that are critical to appropriate encoding of memories). Nicotinic modulation may also act to reduce the impact of distraction and allow more focused attention. For example, nicotinic stimulation may reduce distraction by improving sensory gating in an auditory physiology task (P50) in humans, possibly through α7 stimulation in the hippocampus (Adler et al 1992), or reduce the impact of distraction on the recall of visual information, perhaps through α4β2-induced catecholamine stimulation (Prendergast et al 1998).

Activation of nicotinic receptors in the visual cortex appears to promote intracolumnar inhibition and change the direction of information flow within cortical circuits, enhancing excitatory control of synaptic inputs to pyramidal cells (Xiang et al 1998). Such control, if generalized, may provide an additional mechanism whereby nicotinic stimulation may improve information processing.

These mechanisms may help to control the flow of information into and out of working memory, from the outside or from long-term store, inhibiting irrelevant and augmenting salient information. Alternatively, nicotinic modulation may increase information processing resources nonselectively, improving the performance of effort-demanding tasks, particularly under conditions of impaired functioning such as in AD. Although stimulation of this system is unlikely to restore full function, it may augment remaining cell connections, increasing information (signal) traffic, and therefore improve cognitive function. Preliminary evidence suggests that, although attentional effects can be manifested very rapidly with nicotinic agonists, significant learning and memory effects may need longer administration or exposure to nicotinic agonists than can be provided for by a short-lived single-dose administration.

Straightforward nicotinic receptor activation may not be the sole mechanism whereby nicotinic modulation may improve cognitive functioning. There is some evidence that, under certain conditions, desensitization or functional blockade of nicotinic receptors may enhance performance for certain types of cognitive operations. Evidence from preclinical studies in animals suggests that low doses of the α4β2-antagonist mecamylamine may actually enhance cognitive functioning under some circumstances (Driscoll...
There are hints of this in human studies as well, especially when a nicotinic antagonist is given at low doses to relatively normal functioning individuals (Newhouse et al 1994; P.A. Newhouse et al, unpublished data). Further, there are data showing that the nicotinic antagonist mecamylamine may be as therapeutic as the nicotinic agonist nicotine for patients suffering from Tourette’s syndrome (Sanberg et al 1998). Even the novel nicotinic agonist ABT-418, which we have shown produces therapeutic effects in patients with AD, may act as an antagonist under certain conditions (Papke et al 1997).

A recent study by Fujii and colleagues (Fujii et al 2000) examined the modulatory effect of nicotine on the induction of long-term potentiation (LTP), a synaptic model of learning and memory. These investigators showed that nicotine was able to promote the induction of LTP, apparently by reversing inhibitory postsynaptic potentials produced in the presence of a GABA receptor agonist. Intriguingly, this effect was also seen with the α7 nicotinic antagonist methyllycaconitine, suggesting that nicotinic receptor inactivation or blockade may have been involved in producing the positive effect of LTP. The seeming paradox of both a nicotinic agonist and antagonist producing potentially therapeutic effects may be a specific example of the baseline dependency phenomenon in nicotinic pharmacology (Perkins 1999)—that is, it may be that cognitive and other performance-related operations function best at an optimal level of nicotinic stimulation and that reduction of nicotinic hyperactivity (e.g., Tourette’s syndrome) by blockade or desensitization or an increase in hypoactivity (e.g., AD) by stimulation may be beneficial. Other useful agents may possess nicotinic antagonist properties as well—for example, the antidepressant bupropion, also used for smoking cessation, has been recently shown to possess nicotinic antagonist properties (Fryer and Lukas 1999). However, the use of a nicotinic antagonist such as mecamylamine for AD is less likely to be of benefit because of the left-shift in the dose–response curve for this agent (Newhouse et al 1994), presumably due to the disease-induced loss of nicotinic receptors.

Figure 6 presents a simplified general scheme for how nicotinic stimulation may, through influencing or modulating a broad range of neurotransmitter systems, improve the performance of attentional systems and therefore result in an improvement in learning and/or memory in AD. In this particular diagram, nicotinic-induced release or modulation of several different neurotransmitters is suggested, along with a particular receptor subtype that may be associated with that action. The effects of this transmitter release either separately or together may result in improvement in a number of different cognitive operations affected by, or under the modulatory control of, these neurotransmitters. Generally, this scheme suggests that nicotinic stimulation affects attentional systems either by increasing the absolute activity of those systems or by improving discriminatory or inhibitory functioning (at this time it is not clear whether this increase in activity is due to stimulation or blockade/desensitization of nicotinic receptors). This may lead to improvements in working memory through simply increasing the total amount of attentional resources or more effective partitioning by the so-called central executive (Baddeley 1988), as well as direct improvements in psychomotor speed. The suggested anatomic loci for these effects are by no means exclusive nor are the connections suggested to be definitive. Nonetheless, evidence exists for nicotinic effects on all of these different cognitive operations and/or domains, and therefore such a diagram is a reasonable first step in attempting to synthesize an overall theory of how nicotinic stimulation influences cognitive performance. Note that this scheme pertains completely to the acquisition side of information processing. There is less information regarding nicotinic effects on retrieval of information.

The most likely direct therapeutic role for nicotinic agonists is as augmentation therapy in combination with other agents rather than as monotherapy, except early in disease states or as a prophylactic or preventative treatment. A major problem with nicotinic compounds relates to side effects. Can a compound be developed that is selective in producing improvement in cognition or attention without significant side effects (i.e., with an adequate therapeutic index)? The critical issue is whether a more receptor-specific compound with an improved risk/benefit ratio can be developed.

The treatment of AD has been and continues to be almost exclusively with agents that act predominantly to inhibit acetylcholinesterase. It has been presumed that their therapeutic efficacy is solely mediated by this action. Although partially effective, currently available cholinesterase inhibitors have significant limitations that preclude more than modest therapeutic efficacy. Dose-limiting side effects and nonspecific stimulation of all cholinergic synapses limit both cognitive effects and behavioral benefits (Weinstock 1999). Whether these agents are disease-modifying agents remains to be demonstrated. Other potential disease-modifying strategies have not demonstrated efficacy thus far as monotherapies—for example, antiglaucomatous supplements such as prednisone (Aisen et al 2000), COX-2 inhibitors (Rogers 2000), or hormones such as estrogen (Munard et al 2000). Etiologic strategies, even if they prove effective, are far from clinical implementation. Muscarinic agonists also have not shown efficacy thus far (Thal et al 2000). A new therapeutic strategy is justifiable and necessary.

Nicotinic receptor augmentation may be a worthwhile
strategy to pursue for both symptomatic improvement and disease modification in AD (and perhaps PD as well). Nicotinic stimulation may produce a more rapid onset of cognitive improvement than currently existing cholinesterase inhibitors, as a result of the low threshold necessary for nicotinic receptor-induced phasic stimulation of presynaptic neurotransmitter-releasing receptors or through allosteric modulation of nicotinic receptor function simultaneously with cholinesterase inhibition (Maelicke and Albuquerque 2000). Whether this can be sustained and translates into noticeable clinical improvement remains to be seen. It may be possible to simultaneously directly and/or indirectly stimulate nicotinic receptors while inhibiting cholinesterase function through the use of agents that have simultaneous cholinesterase inhibition effects and nicotinic allosteric effects (e.g., galantamine, phystostigmine). This may lead to enhanced cholinergic activity in those regions activating cognitive operations that are cholinergically modulated. This may in turn increase information processing resources and allow greater throughput (useful cognitive work per unit time).

Potentially more rapid onset of effects with nicotinic agonists relative to cholinesterase inhibitors alone may be a result of the necessary pharmacokinetic and pharmacodynamic properties that a cholinesterase inhibitor must have to be tolerable (i.e., slow onset of cholinergic enhancement to avoid intolerable side effects due to nonspecific cholinergic stimulation). The fact that many patients do respond favorably, albeit slowly, to cholinesterase inhibitors suggests that the cholinergic system is
still plastic enough to respond to treatment. Nicotinic stimulation may be orthogonal or synergistic to cholinesterase inhibition rather than duplicative. In a recent preclinical study of animal learning, nicotinic agonist treatment has been shown to enhance the positive effects of cholinesterase inhibitors on cognitive performance (Bencherif 1999). This suggests it may be possible to enhance cholinergic functioning with nicotinic agents in combination with cholinesterase inhibitors to a greater degree than with cholinesterase inhibitors alone.

In addition to AD, changes in CNS cholinergic–nicotinic systems have also been shown to occur in the brains of patients with PD. In particular, a similar loss of cholinergic cells in the basal forebrain nuclei, as occurs in AD, has been described in PD (Whitehouse et al 1983). The loss of cholinergic markers in the cortex (Perry et al 1995) that occurs in PD may be related to lesions in these nuclei and other cholinergic projections to the cortex (Whitehouse et al 1988). Studies have shown a marked reduction in cortical nicotinic receptor binding that parallels the degree of dementia in PD and increasing age (Aubert et al 1992; Whitehouse et al 1988). There is similarity between the cortical nicotinic binding site loss in PD and AD as well as similar changes in other cholinergic markers.

We have recently examined the quantitative effects of nicotine in a pilot study in PD patients (Kelton et al 2000). Subjects showed positive effects on motor and cognitive performance both acutely and after 2-week transdermal nicotine administration. Further double-blind studies are necessary to confirm these results, but if they are, this would provide optimism that nicotinic stimulation may be an additional strategy for PD treatment, either by utilizing nicotinic agonists as monotherapy in early cases or as a dopa-augmenter or dopa-sparing drug in later stage disease.

The development of selective nicotinic agents for human use has made substantial progress in the last decade (Lloyd and Williams 2000). A variety of agents have been and are being tested in humans for a variety of indications including AD, PD, attention-deficit/hyperactivity disorder, schizophrenia, Tourette’s syndrome, and pain. Whether long-term benefit can be obtained from these agents will be a test of both pharmaceutical development and clinical relevance. A potential alternate method for stimulating nicotinic receptor function is through allosteric modulation of sites on the receptor complex physically distinct from the agonist recognition site (Maelicke and Albuquerque 2000). Although enhancement of nicotinic receptor function by this mechanism utilizing cholinesterase inhibitors has been demonstrated in vitro (Maelicke and Albuquerque 2000), there is so far a lack of in vivo or human data suggesting these effects can be detected separately from the more direct effects of these agents.

If by direct stimulation or allosteric modulation such activity translates into increased nicotinic receptor activity, not only may more rapid or more extensive cognitive benefit result in the short run, but other effects such as cytoprotection or disease stabilization may be manifest with long-term stimulation (based on the data suggesting that nicotinic stimulation may be cytoprotective against β-amyloid toxicity) (Kihara et al 1997; Zamani et al 1997).

Conclusions

A decade and a half of remarkable basic scientific work has resulted in substantial progress in understanding the molecular structure, neuroanatomy, distribution, and physiology of CNS nicotinic receptors (Paterson and Nordberg 2000). Understanding of their functional role in human physiology, cognitive and behavioral psychology, and human pathologies has, however, lagged behind, due in large measure to technical difficulties in the study of these functions in humans and the lack of ideal pharmacologic, imaging, and cognitive tools for the analysis and assessment of their properties. This latter situation is now beginning to change as the ability to image nicotinic receptor subtypes in the human brain becomes possible with more selective ligands (Silvey et al 1999), increasingly sophisticated electrophysiologic techniques being applied (Adler et al 1992, 1993), more selective cognitive paradigms developed, and the availability of more subtype-selective nicotinic agonists (Lloyd and Williams 2000) and allosteric modulators for human use that will allow a more precise definition of nicotinic receptor contribution to attention, learning, memory, and behavior.

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