
Cognitive Effects of Nicotine

Amir H. Rezvani and Edward D. Levin

Nicotine and other nicotinic agonists have been found to improve performance on attention and memory tasks. Clinical studies using nicotine skin patches have demonstrated the efficacy of nicotine in treating cognitive impairments associated with Alzheimer's disease, schizophrenia, and attention-deficit/hyperactivity disorder. Experimental animal studies have demonstrated the persistence of nicotine-induced working memory improvement with chronic exposure, in addition to the efficacy of a variety of nicotinic agonists. Mechanistic studies have found that $\alpha 7$ and $\alpha 4\beta 2$ nicotinic receptors in the hippocampus are critical for nicotinic involvement in cognitive function. Clinical and experimental animal studies provide mutually supporting information for the development of novel nicotinic therapies for cognitive dysfunction. Biol Psychiatry 2001;49:258–267 © 2001 Society of Biological Psychiatry

Key Words: Nicotine, attention, AD, memory, ADHD, cognition

Introduction

Nicotinic cholinergic systems in the brain have been implicated in several aspects of some important mental diseases such as Alzheimer's disease (AD), attention-deficit/hyperactivity disorder (ADHD), and schizophrenia. Both clinical experiments and animal studies support the role of central nicotinic systems in learning, memory, and cognition. Nicotine is the prototypic nicotinic acetylcholine receptor (nAChR) agonist, which may enhance cognition by direct effects on attention and by interacting with the presynaptic nAChR to facilitate the release of ACh, glutamate, dopamine, norepinephrine, serotonin, and γ -aminobutyric acid, the neurotransmitters that have been implicated in learning and memory (Samuels and Davis 1998; Wonnacott 1997). In a variety of experiments, nicotine has been shown to enhance attention and improve learning (Levin and Simon 1998). Nicotine and nicotinic agents also have been shown to possess

neuroprotective effects, which are probably mediated by stimulation of the $\alpha 7$ nicotinic receptors. Recently, it has been shown that nicotine may act to inhibit the deposition of β -amyloid in vitro (Salomon et al 1996). Nicotine can be administered to patients with cognitive dysfunction via skin patch or injection to assess efficacy, as a proof of principle, for possible treatments to improve cognitive performance. We have used this strategy to demonstrate the efficacy of nicotine treatment in several different populations including normal nonsmoking adults, patients with AD, schizophrenic patients, and adults with ADHD. Animal models can also be used to determine the efficacy of nicotinic treatment for improving cognitive functions. Importantly, mechanisms of nicotinic action can be determined with animal models using selective nicotinic ligands, local infusion, and lesions. Finally, experimental animal models are important for the initial assessment of efficacy of novel nicotinic drugs. Parallel clinical and experimental animal studies provide mutually important information for the development of nicotinic treatments for cognitive dysfunction.

Clinical Studies

The clearest effect of nicotine improving cognition in humans is with attentional processes. In a series of studies, we have examined the effects of nicotine skin patch treatment on attentional performance, as indexed by a computerized continuous performance task (CPT) assessing attentional performance.

Normal Adult Nonsmokers

Baseline effects of nicotine on attentional function can be studied in normal, nonsmoking adults. This type of study avoids the problem of smokers experiencing withdrawal from nicotine, since withdrawal from nicotine in deprived smokers causes attentional impairments (Hatsukami et al 1989), which may cloud the interpretation of the nicotine effects on attention. Warburton and colleagues have found cognitive improvements with nicotine administration in smokers in the absence of withdrawal effects (Warburton and Arnall 1994; Warburton and Mancuso 1998). However, there is still a question concerning whether nicotine

From the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina.

Address reprint requests to Amir H. Rezvani, Ph.D., Department of Psychiatry, Neurobehavioral Research Laboratory, Box #3412, Duke University Medical Center, Durham NC 27710.

Received May 22, 2000; revised October 5, 2000; accepted October 18, 2000.

can improve attentiveness in normal nonsmokers who have no pre-existing attentional impairment. Thus, it seems that the best way to determine the effects of nicotine without the potential effect of smoking withdrawal is to conduct studies in normal adult nonsmokers. In addition, normal nonsmoking adults provide an important group for understanding nicotine effects on normal cognitive performance, relative to effects in reversing impaired performance as discussed below.

In an attempt to determine the effect of transdermal nicotine on attention, adult nonsmoking subjects without ADHD symptoms were administered either placebos or 7-mg/day nicotine patches (NicoDerm, SmithKline Beecham, Philadelphia) for 4.5 hours during a morning session (Levin et al 1996b, 2000). This dose was chosen to minimize the side effects of nausea and dizziness in the nonsmokers. Measures of treatment effect included the Profile of Mood State, Conners' computerized CPT (Conners et al 1996) of attentiveness, and a computerized interval timing task. In the Conners' CPT, the errors of omission (to skip to respond) demonstrate that variability of response times is sensitive to sustained attention and is increased by attentional lapses. Errors of commission (responding when you should refrain) are sensitive to impulsivity (i.e., the degree of behavioral inhibition). Our results showed that administration of 7 mg/day via a transdermal nicotine patch significantly reduced the number of errors of omission on the CPT task (Figure 1A). In this study there was no nicotine-induced increase in errors of commission, providing evidence that the nicotine-induced decrease in errors of omission was not merely due to a shift in response strategy to increased response rate (Levin et al 1998b). It was also found that nicotine patch treatment significantly decreased response time variability (Figure 1B) and increased the composite attention measure. However, there was no significant effect of nicotine patch on reaction time on the CPT.

Overall, this study showed that nicotine given via a transdermal patch could significantly improve attention in nonsmoking subjects who had no pre-existing attentional problems. These findings are in agreement with other clinical studies demonstrating nicotine-induced attentional improvements in a variety of mental cognitive disorders such as AD (Sahakian and Jones 1991), ADHD (Conners et al 1996; Levin et al 1996b, 1996e), and schizophrenia (Levin et al 1996e). Nicotine-induced memory improvements are also seen in unaffected adults (Rusted et al 1995; Williams 1980). This effect has recently been shown to be specific to tasks with explicit effortful memory demands (Rusted et al 1998). Memory consolidation in particular has been shown to improve with nicotine administration (Colrain et al 1992).

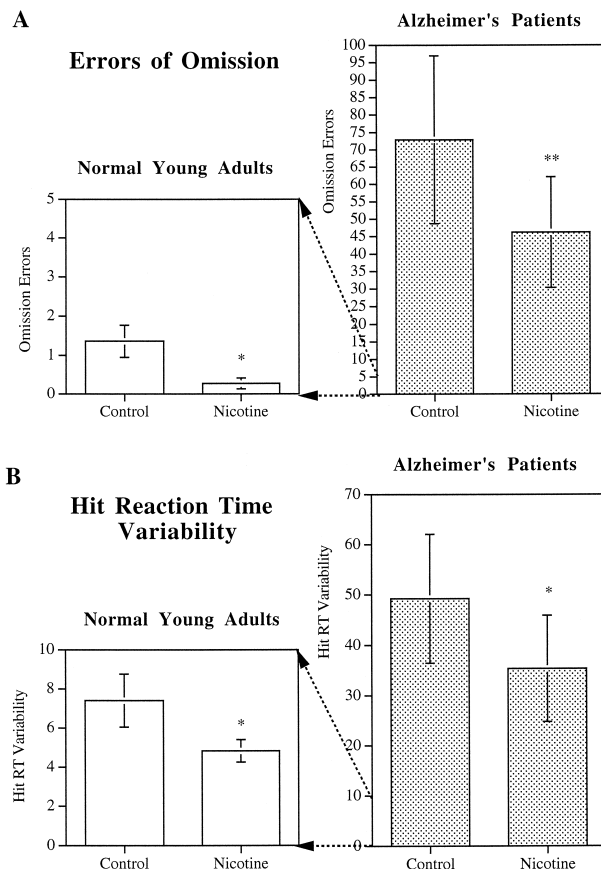


Figure 1. Comparison of the effects of nicotine administration on errors of omission and hit reaction time (RT) variability in normal young adults and Alzheimer disease patients. Continuous performance task mean errors of omission and hit RT variability were averaged over all nicotine and placebo sessions ($*p < .05$ when compared with control; $**p < .025$ when compared with control). Errors of omission are significantly higher in AD patients (73 vs. 45). Nicotine administration by patch significantly reduced errors of omission in both normal subjects and AD patients (A). Hit RT variability is also greater in AD patients (49 vs. 35). Again, nicotine administration by patch significantly reduced RT variability in both normal subjects and AD patients (B).

Alzheimer's Disease

More than 4 million Americans suffer from AD, which has been described as a disease of cholinergic innervation and is characterized by marked degeneration in cortical nicotinic cholinergic receptor binding relative to age-matched control subjects (Coyle et al 1983). Unfortunately, current treatment options are limited to the use of acetylcholinesterase (AChE) inhibitors, including tacrine and donepezil, which indirectly provide stimulation of cholinergic neurons in the central nervous system (Standaert and Young 1996), and possibly some antioxidants (Samuels and Davis 1998). However, there is evidence that direct stimulation of nicotinic receptors in the brain may also provide

improvement in people with AD. A loss of nicotinic binding sites, especially in the cortex and hippocampus, has been reported in patients with AD (Giacobini et al 1988; Kellar and Wonnacott 1990; Newhouse et al 1997; Nordberg 1993, 1995; Nordberg et al 1988; Perry et al 1987; Quirion et al 1986; Rinne et al 1991; Schroder et al 1995; Shimohama et al 1986; Sugaya et al 1990). Nicotine administration via injection or skin patches has been shown to significantly improve attention (Jones et al 1992; Sahakian and Jones 1991; White and Levin 1999), learning (White and Levin 1999), and memory (Newhouse et al 1988; Parks et al 1996) in patients with AD (for a review, see Newhouse et al 1997). Wilson and coworkers (Wilson et al 1995) have shown that nicotine administered via nicotine skin patches significantly improves learning in AD patients.

In a double-blind, placebo-controlled study six patients with probable AD were exposed to 7, 8, and 7 days of a placebo, nicotine, and washout, respectively, and their learning, memory, and behavior were evaluated. Although the number of subjects was limited to six individuals, the data showed that sustained transdermal delivery of nicotine (22-mg nicotine patch, delivering approximately 0.9 mg nicotine/hour over a 24-hour period) improved performance on a nonverbal learning task (repeated acquisition) during the nicotine condition, which persisted throughout the washout. Although memory and global cognition were not significantly affected in this study (Wilson et al 1995), Newhouse and colleagues (1988) have demonstrated that nicotine injections improve memory performance in AD patients. However, Snaedal and colleagues (1996) were unable to find a significant effect of 4 weeks of transdermal nicotine delivery on memory in 18 AD patients, possibly due to a significant placebo effect, as patients on both nicotine and the placebo showed improvement in short-term memory.

To further investigate the therapeutic potential of nicotine in AD, we have conducted a study to evaluate the clinical and neuropsychologic effects of chronic transdermal nicotine in AD patients over a 4-week period. The double-blind, placebo-controlled, crossover study consisted of two 4-week periods separated by a 2-week washout period. Patients wore the nicotine patch (Nicotrol, Pharmacia, Peapack, NJ) for 16 hours/day at the following doses: 5 mg/day during week 1, 10 mg/day during weeks 2 and 3, and 5 mg/day during week 4. A total of eight patients (three male and five female) with mild to moderate AD symptoms were studied. Nicotine treatment significantly improved attention performance as measured by the CPT. Similar to studies in normal adults, it was found that nicotine skin patches significantly reduced errors of omission on the CPT in patients with AD (Figure 1A). Also, as with the normal nonsmoking adults, no nicotinic

effect on errors of commission was seen, providing evidence that the nicotine-induced decrease in omission errors was due not only to a shift in more frequent responding (White and Levin 1999), but also to a true increase in response accuracy, suggesting improvement in attention by nicotine treatment. Performance of the Alzheimer's patients on the CPT varied considerably, but nicotine treatment consistently caused an improvement in all patients. Performance accuracy improved from 5% to 80%. In the Alzheimer's patients nicotine treatment also significantly decreased the variability of hit response time (Figure 1B). Importantly, the improvement in the AD patients persisted for the 4 weeks of nicotine administration. This finding is similar to the persistence of effect we have seen in our chronic studies with rats. However, the nicotine patch did not improve performance on other tests that measured motor and memory function, which brings the clinical impact of nicotine treatment in AD into question (White and Levin 1999). In another study, Wilson and colleagues (1995) found a positive effect of nicotine skin patch administration by persisting for at least 8 days of continued administration. Persistence of treatment efficacy is a necessary part of any treatment for a chronic disorder such as AD, and the fact that nicotine exhibits such a long-lasting effect makes it more suitable for consideration as a potential treatment for AD (Levin and Rezvani 2000).

Adults with Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder is characterized by impaired attentiveness, increased impulsivity, and hyperactivity. It is a relatively common cognitive impairment classically seen in children and adolescents, but is now recognized to exist in adults as well. The high prevalence of smoking among adolescents and adults with ADHD suggests that patients with ADHD may smoke as a form of self-medication for their symptoms. Cigarette smoking and nicotine administration have been shown to improve attentiveness (Levin 1992). We have found that nicotine skin patch treatment causes significant reductions ($p < .005$) in clinical signs of the severity of attentional deficit, as measured by the benchmark Clinical Global Impressions Scale (Conners et al 1996; Levin et al 1996b). In a placebo-controlled, double-blind study six smokers and 11 nonsmoking adults with ADHD symptoms were given either a placebo patch or a nicotine patch (7 mg/day for nonsmokers and 21 mg/day for smokers) for 4.5 hours during a morning session. Active and placebo patches were given in a counterbalanced order approximately 1 week apart. Nicotine administration, compared with the placebo, caused a significant improvement on the Clinical

Global Impressions Scale in both smokers and nonsmokers, suggesting that the effect was not due merely to withdrawal relief. In the CPT, nicotine skin patch treatment was also found to significantly reduce the variability of response speed over the different blocks of the test session (i.e., improvement in attentional consistency). In ADHD adults, nicotine did not cause significant effects in either errors of omission or errors of commission, as it did in normal adults and patients with AD. In accordance with these findings, in a recent study Wilens and coworkers (1999) found that the novel nicotinic agonist ABT-418 also effectively improves symptoms of inattention in adults with ADHD.

Overall, these clinical studies demonstrated that nicotine given via a skin patch could significantly improve symptoms of ADHD. However, the mechanisms for nicotine effects in improving the symptoms of ADHD are not fully understood. Nicotine has effects of potentiating dopamine release, which has a similar net effect of increasing dopamine stimulation, as do methylphenidate and amphetamine, currently used in ADHD treatment. Nicotine also has a variety of actions on other neuronal systems including cholinergic, serotonergic, and noradrenergic systems, and it is possible that it exerts its action on cognition by modulating these neuronal systems. Studies using nicotinic agonists that have different subtype specificity should help better understanding of nicotine's mechanism of action on cognition. Nicotine agonists or nicotine administered in a less hazardous form than cigarette smoking, such as a skin patch, may present therapeutic potentials for ADHD. For better understanding of the mechanism of action of nicotine and its ultimate therapeutic values for the treatment of ADHD, more clinical trials with ADHD are needed.

Schizophrenic Patients

Altered cholinergic systems have been reported and implicated in people afflicted with schizophrenia (Arneric 2000). People with schizophrenia smoke cigarettes at a very high rate—about 80–90%, as compared with 45–70% of patients with other psychiatric disorders and 33% of the general population (Hughes et al 1996). There is evidence that they may be self-medicating with cigarettes to attenuate cognitive dysfunction resulting from schizophrenia and antipsychotic medication. Schizophrenic patients have been shown to have a deficient number of nicotinic receptors, especially in the hippocampus (Freedman et al 1995; Leonard et al 1996), which may be an underlying factor in their cognitive impairment. Sensory gating is a hippocampal phenomenon that is impaired in schizophrenic patients (Adler et al 1993). In individuals without psychiatric illness, the evoked response to a

second stimulus in a pair of stimuli is less than the response to the first one. Schizophrenic patients typically have a higher ratio for the second response, suggesting a decreased gating of neuronal responses to auditory stimuli (Arneric 2000). Cigarette smoking has been shown to diminish this impairment (Adler et al 1993).

To further our understanding we have studied the effect of nicotine treatment on cognitive function in schizophrenic patients. The experiment was conducted in a double-blind fashion to assess the interactions of the nicotine skin patch and the antipsychotic drug haloperidol on cognition performance in a group of smoking schizophrenic subjects. The cognitive effects of 0-, 7-, 14-, and 21-mg/day nicotine skin patches were examined with three different dose levels of haloperidol. Three hours after administration of the skin patch the patients were given a computerized cognitive test battery and the Conners' CPT. Administration of nicotine via skin patch caused a dose-related reduction in CPT response speed variability in all haloperidol-dose groups. Nicotine treatment also attenuated the haloperidol-induced deficits in a delayed matching to sample (DMTS) working memory test (Levin et al 1996e). Thus, these data demonstrate that nicotine administration can reduce some of the adverse effects of haloperidol and the cognitive impairment of schizophrenia itself. Although the mechanisms of action of nicotine in improving cognition in schizophrenia are not well understood, it is likely that nicotine exerts its improving effect by releasing dopamine (Wonnacott et al 1989). Indeed, Decina and coworkers (1990) have demonstrated that schizophrenic patients who smoke have significantly lower rates of neuroleptic-induced Parkinsonism.

Experimental Animal Studies

Animal models have proved useful not only in the functional testing of novel nicotine compounds, but also in understanding the mechanisms for nicotine-induced cognitive improvement. Nicotine involvement in learning processes in rodents has been recognized for several decades. For the past decade we have studied the involvement of nicotinic systems in memory functions using animal models. Both acute and chronic nicotine treatments have been shown to improve working memory function in rats, using the radial arm maze. This test is a standard and sensitive measure of working memory performance in an eight-arm maze. *Working memory* is defined as memory with changing contents, as opposed to *reference memory*, which is defined as memory with fixed contents (Levin et al 1996c). Working memory can be differentiated from reference memory in the radial arm maze by always baiting the same arms at the beginning of each session. Entries into baited arms are considered working memory

and entries into nonbaited arms are considered reference memory. Usually a 16-arm radial maze is used for assessing working and reference memory. This technique has been used to show the relative specificity of nicotine-induced improvement in working but not reference memory (Levin et al 1997b). Baiting 12 of the 16 arms presents a difficult working memory task, while still leaving four arms that are never baited for the assessment of reference memory.

Acute Nicotine and Memory

A variety of studies have shown that acute treatment with nicotine or nicotinic agonists can improve working memory function in the radial arm maze in rats (Decker et al 1995; Levin and Simon 1998; Levin and Torry 1995). The following experiments were conducted to assess the effect of acute nicotine administration on both working and reference memory function in adult female rats. After a standard 18-session training in the 16-arm radial maze, rats were injected subcutaneously with either saline or a dose of 0.2 mg/kg nicotine, and 20 min later their performance was assessed. In six separate studies with a total of 71 adult female Sprague–Dawley rats, we found that a single dose of 0.2 mg/kg nicotine injected subcutaneously 20 min before testing significantly improved working memory. The choice accuracy (entries to repeat—i.e., the number of correct entries into the arms until an error is made), which indicates the working memory, was significantly increased following nicotine administration in rats (Levin et al 1997b).

It also has been found that acute treatment with other selective nicotinic agonists, such as dimethylaminoethanol (Levin et al 1995), epibatidine (Levin et al 1996d), isonicotine, norisonicotine (Levin et al 1999b), AR-R 17779 (Levin et al 1998a), ABT-418 (Decker et al 1994; Terry et al 1997), or lobeline (Decker et al 1993; Rochford et al 1996; Terry et al 1996) significantly improves memory performance (Levin and Simon 1998). Acute nicotine administration has also been shown to facilitate retention of avoidance training (Brioni and Arneric 1993; Zarrindast et al 1996) and enhance Morris water maze performance in young and aged rats (Socci et al 1995). Acute nicotine treatment has been shown to reverse DMTS performance caused by aging and facilitates performance in aged rats exhibiting deficits in spatial working memory (Cregan et al 1989; Levin and Torry 1996) or poor passive avoidance performance due to a choline-deficient diet (Sasaki et al 1991).

Chronic Nicotine and Memory

From a therapeutic point of view, it is crucial for a drug that is effective in an acute form to remain efficacious with

repeated administration also. To investigate the efficacy of chronic administration of nicotine on working memory, the following experiments were carried out. After a standard 18-session training on the radial arm maze, rats were implanted subcutaneously with an osmotic minipump delivering 5 mg/kg/day nicotine or an equal volume of saline for 28 consecutive days, or a nicotine pellet delivering 12 mg/kg/day for 21 consecutive days. Working memory was assessed during the weeks of nicotine delivery and up to 2 weeks after the termination of nicotine delivery. In seven separate studies it was found that chronic administration of both 5- and 12-mg/kg/day nicotine significantly and consistently improved memory performance on the eight-arm radial maze in adult female rats (Levin et al 1990, 1996a; Levin and Torry 1996). However, only the higher dose of 12 mg/kg/day induced a persistent effect, even 2 weeks after the termination of nicotine delivery.

In a follow-up study using a 16-arm radial maze it was found that chronic administration of 5 mg/kg/day nicotine induced facilitation that was specific for working memory but not reference memory (Levin et al 1996c). This selective effect of nicotine in improving working memory but not reference is consistent with both acute and chronic nicotine administrations. Chronic treatment with nicotinic agonists also improves memory performance in other memory tasks, such as one-way avoidance and the Lashley III maze (Arendash et al 1995b). However, chronic nicotine treatment does not appear to be effective in the T-maze alteration task (Levin et al 1997a). This may be related to the effect of nicotine proactive interference (Dunnett and Martel 1990). It has been shown that memory improvements found with chronic nicotine treatment can be blocked by chronic coadministration of the nicotine antagonist mecamylamine (Levin et al 1993a) but not by acute administration (Levin and Rose 1990).

Chronic nicotine infusion can also reverse working memory deficits due to lesions of fimbria and medial basolateral projection (Levin et al 1993b). However, chronic nicotine administration does not appear to facilitate working memory performance in aged rats, possibly due to the decrease in functional nicotinic receptors in aged animals (Arendash et al 1995a, 1995b; Levin and Torry 1996).

Hippocampal Nicotinic Involvement in Memory Function

The hippocampus has long been known to be involved in attention and memory (Jarrard 1995). It has been shown that hippocampal ACh increases significantly in rats that have learned a task relative to matched control rats

(Stancampiano et al 1999). Nicotine facilitates hippocampal synaptic activity (Gray et al 1996) and increases hippocampal long-term potentiation (Hamid et al 1997). The hippocampus may also be an important site for nicotine effects on memory. Cholinergic neurons in the medial septum and diagonal band send projections via the fimbria–fornix to innervate the hippocampus, and high concentrations of nicotinic receptors have been found in the hippocampus (Martin and Aceto 1981; Schwartz 1986). For example, the $\alpha 7$ type of nicotinic receptor is found in high concentration in the rat hippocampus (Clarke et al 1984; Freedman et al 1993), and although little is currently known about the functional role of $\alpha 7$ -type nicotinic receptors in the hippocampus, they may be involved in the hippocampal processing of information.

To investigate the role of hippocampal structure in nicotine effect on memory, two approaches have been adopted in this laboratory: local infusions of nicotinic antagonists and lesioning of the hippocampus.

HIPPOCAMPAL LOCAL INFUSIONS. In local infusion studies we examined the effects of several nicotinic antagonists infused into the ventral hippocampus on choice accuracy, using a radial arm maze. In the first study (Kim and Levin 1996), after standard 18-session training on the radial arm maze adult female rats ($n = 16$) were implanted with bilateral cannulae for acute infusion of the drug into the ventral hippocampus. One week after recovery from surgery, a dose of mecamylamine (0, 1, 3.3, or 10 $\mu\text{g}/\text{side}$) was infused into the ventral hippocampus. Ten minutes later memory performance was assessed using a radial arm maze. Acute ventral hippocampal local infusion of mecamylamine, a noncompetitive nicotinic antagonist, caused significant memory deficit by reducing choice accuracy in the radial arm maze. However, as opposed to systemic administration, local infusion of mecamylamine into the ventral hippocampus did not affect response latency. Consistent with our findings, local infusions of mecamylamine into the hippocampus were also found to impair working memory performance, but not reference memory performance, in rats (Ohno et al 1993).

In follow-up studies, the effects of intrahippocampal infusion of the selective $\alpha 4\beta 2$ nicotinic antagonist dihydro- β -erythroidine (DH β E) ($n = 8$) and selective $\alpha 7$ antagonist methyllycaconitine (MLA) ($n = 8$) in two sets of rats trained on the eight-arm radial maze were assessed. Both DH β E and MLA caused significant memory impairments after infusion into the ventral hippocampus (Felix and Levin 1997). Thus, it seems that both $\alpha 4\beta 2$ and $\alpha 7$ nicotinic receptor subtypes in the hippocampus may be important for working memory function (Levin and Rezvani 2000).

HIPPOCAMPAL LESIONS. Lesion models have also provided evidence in support of nicotinic hippocampal involvement in cognitive function. It has been shown that nicotine administration reverses attentional and memory impairments caused by basal forebrain lesions in rats (Grigoryan et al 1994, 1996; Muir et al 1995) and marmosets (Ridley et al 1986).

In lesion studies we conducted a series of experiments to determine the importance of ventral hippocampal neurons for the chronic nicotine-induced memory improvement. Forty adult female rats were trained on the working memory task for 18 sessions in an eight-arm radial maze. After acquisition, they were sorted into four matched groups—sham lesion/no nicotine ($n = 10$), sham lesion/nicotine ($n = 10$), hippocampal lesion/no nicotine ($n = 9$), and hippocampal lesion/nicotine ($n = 11$)—and received subcutaneous implants of an osmotic minipump that delivered either nicotine at a dose of 5 mg/kg/day or vehicle. After recovery, rats were tested again on the radial arm maze three times per week for 4 consecutive weeks. Small hippocampal lesions were made with ibotenic acid microinjected into the ventral hippocampus (Levin et al 1999a). Consistent with previous findings, these results show that in the sham-lesioned group chronic nicotine infusion caused a significant improvement in choice accuracy. In contrast, small ibotenic acid-induced lesions of the ventral hippocampus prevented nicotine-induced memory improvement in rats. Analysis of the simple main effects of nicotine in the sham-operated and -lesioned groups showed a significant nicotine-induced improvement of working memory in the sham-operated rats but not in the lesioned group. Interestingly, the lesion-induced blockade of the nicotine effect was apparent even though the lesion itself did not significantly impair working memory performance (Levin et al 1999a). In a previous study, we found that the knife-cut lesion of the fimbria–fornix, which carries cholinergic innervation to the hippocampus, did not eliminate chronic nicotine-induced memory improvement (Levin et al 1993b). Thus, it appears that the critical nicotinic receptors in the hippocampus are not on the synaptic endings of the ACh septohippocampal projection.

Conclusions

Nicotine is best known as the principal psychoactive chemical in tobacco. As such, it is an important component of tobacco addiction. However, nicotine, like other drugs, has a spectrum of effects. In addition to its addiction liability, nicotine is similar to morphine in that it has effects that may be therapeutically useful. Nicotinic systems in the brain play an important role in the neural basis of memory and attention and have been implicated in mental diseases such as AD and schizophrenia. Clinical

studies using nicotine skin patches have demonstrated that nicotine treatment can improve cognitive performance in a variety of groups: normal nonsmoking adults, AD patients, schizophrenics, and adults with ADHD. The improvement is seen principally in terms of improved attentional performance. Importantly, the nicotine-induced memory improvement does not diminish with chronic administration and has been seen to persist after withdrawal. In experimental studies using animal models, working memory improvements have been demonstrated with acute and chronic nicotine treatment, as well as treatment with a variety of other nicotinic agonists. Mechanistic studies have also revealed the involvement of $\alpha 7$ and $\alpha 4\beta 2$ nicotinic receptors in the effects on working memory function in the hippocampus. The clinical studies with nicotine skin patches have provided encouraging initial evidence concerning the promise of the nicotinic approach to cognitive therapeutics, whereas the experimental animal studies have provided important basic information concerning the critical mechanisms of nicotinic involvement in cognition and the efficacy of novel nicotinic drugs. Nicotine, or nicotinic compounds with more selective effects, may therefore be of some value in treating cognitive dysfunction associated with AD, ADHD, and schizophrenia. However, it should be remembered that the effects of nicotine, like the effects of other cholinergic treatment approaches in AD, may decrease with disease progression and the associated decline in cholinergic neurons (Levin and Torry 1996; Samuels and Davis 1998). Because AD is a multifactorial disease and several neuronal systems have been implicated in its manifestation, future therapeutic approaches may include various combinations of cholinergic, adrenergic, and glutaminergic drugs, antioxidants, and agents that alter amyloid processing (Samuels and Davis 1998).

In addition to nicotine and nicotinic agents, some relatively new cholinergic agents have shown promise in improving AD symptoms. For example, galantamine, a competitive reversible AChE inhibitor that has no effect on butyrylcholinesterase (Pacheco et al 1995), acts at allosteric nicotinic sites and enhances its cholinergic activity (Samuels and Davis 1998). Recently, it has been shown that galantamine significantly improved cognitive, functional, and behavioral symptoms of AD relative to a placebo (Raskind et al 2000; Tariot et al 2000). Like any drug effect, nicotine actions on cognitive function are limited, and some studies have not been able to demonstrate nicotine-induced improvement in cognition (Heishman et al 1994).

The novel insights arising from these works are the consistent improvement in attentional performance seen in normal nonsmoking adults, adults with ADHD, schizophrenic individuals, and people with AD. The animal data

are complementary, showing that the hippocampus is a critical target for nicotine's cognitive effects. However, the ultimate therapeutic value of nicotine and nicotinic compounds for the treatment of cognitive dysfunction needs to be evaluated in larger clinical trials.

Supported in part by National Institute on Drug Abuse Grant No. DA 11943.

The authors thank Rita Gross and Kerri Robertson for reviewing the manuscript.

Aspects of this work were presented at the symposium "Nicotine Mechanisms in Alzheimer's Disease," March 16–18, 2000, Fajardo, Puerto Rico. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant provided by Janssen Pharmaceutica LP.

References

- Adler LE, Hoffer LD, Wiser A, Freedman R (1993): Normalization of auditory physiology by cigarette smoking in schizophrenic patients. *Am J Psychiatry* 150:1856–1861.
- Arendash GW, Sanberg PR, Sengstock GJ (1995a): Nicotine enhances the learning and memory of aged rats. *Pharmacol Biochem Behav* 52:517–523.
- Arendash GW, Sengstock GJ, Sanberg PR, Kem WR (1995b): Improved learning and memory in aged rats with chronic administration of the nicotinic receptor agonist GTS-21. *Brain Res* 674:252–259.
- Arneric SP (2000): Neurobiology and clinical pathophysiology of neuronal nicotinic acetylcholine receptors. In: Piasecki M, Newhouse PA, editors. *Nicotine in Psychiatry: Psychopathology and Emerging Therapeutics*. Washington, DC: American Psychiatric Press, 3–35.
- Brioni JD, Arneric SP (1993): Nicotinic receptor agonists facilitate retention of avoidance training—participation of dopaminergic mechanisms. *Behav Neural Biol* 59:57–62.
- Clarke PBS, Pert CB, Pert A (1984): Autoradiographic distribution of nicotine receptors in rat brain. *Brain Res* 323:390–395.
- Colrain IM, Mangan GL, Pellett OL, Bates TC (1992): Effects of post-learning smoking on memory consolidation. *Psychopharmacology* 108:448–451.
- Connors CK, Levin ED, Sparrow E, Hinton SC, Erhardt D, Meck WH, et al (1996): Nicotine and attention in adult ADHD. *Psychopharmacol Bull* 32:67–73.
- Coyle JT, Price DL, DeLong MR (1983): Alzheimer's disease: A disorder of cholinergic innervation. *Science* 219:1184–1190.
- Cregan E, Ordy JM, Palmer E, Blosser J, Wengenack T, Thomas G (1989): Spatial working memory enhancement by nicotine of aged Long-Evans rats in the T-maze. *Soc Neurosci Abstr* 15:731.
- Decina P, Caracci G, Sandik R, Berman W, Mukherjee S, Scapicchio P (1990): Cigarette smoking and neuroleptic-induced Parkinsonism. *Biol Psychiatry* 28:502–508.
- Decker MW, Brioni JD, Bannon AW, Arneric SP (1995): Diversity of neuronal nicotinic acetylcholine receptors: Lessons from behavior and implications for CNS therapeutics—minireview. *Life Sci* 56:545–570.

- Decker MW, Curzon P, Brioni JD, Arneric SP (1994): Effects of ABT-418, a novel cholinergic channel ligand, on place learning in septal-lesioned rats. *Eur J Pharmacol* 261:217–222.
- Decker MW, Majchrzak MJ, Arneric SP (1993): Effects of lobeline, a nicotinic receptor agonist, on learning and memory. *Pharmacol Biochem Behav* 45:571–576.
- Dunnett SB, Martel FL (1990): Proactive interference effects on short-term memory in rats: I. Basic parameters and drug effects. *Behav Neurosci* 104:655–665.
- Felix R, Levin ED (1997): Nicotinic antagonist administration into the ventral hippocampus and spatial working memory in rats. *Neuroscience* 81:1009–1017.
- Freedman R, Hall M, Adler LE, Leonard S (1995): Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. *Biol Psychiatry* 38:22–33.
- Freedman R, Wetmore C, Stromberg I, Leonard S, Olson L (1993): Alpha-Bungarotoxin binding to hippocampal interneurons—immunocytochemical characterization and effects on growth factor expression. *J Neurosci* 13:1965–1975.
- Giacobini E, DeSarno P, McIlhany M, Clark B (1988): The cholinergic receptor system in the frontal lobe of Alzheimer's patients. In: Clementi F, Gotti C, Sher E, editors. *Nicotinic Acetylcholine Receptors in the Nervous System*. Berlin: Springer-Verlag, 367–378.
- Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA (1996): Hippocampal synaptic transmission enhanced by low concentrations of nicotine. *Nature* 383:713–716.
- Grigoryan G, Hodges H, Mitchell S, Sinden JD, Gray JA (1996): 6-OHDA lesions of the nucleus accumbens accentuate memory deficits in animals with lesions to the forebrain cholinergic projection system: Effects of nicotine administration on learning and memory in the water maze. *Neurobiol Learn Memory* 65:135–153.
- Grigoryan GA, Mitchell SN, Hodges H, Sinden JD, Gray JA (1994): Are the cognitive-enhancing effects of nicotine in the rat with lesions to the forebrain cholinergic projection system mediated by an interaction with the noradrenergic system? *Pharmacol Biochem Behav* 49:511–521.
- Hamid S, Dawe GS, Gray JA, Stephenson JD (1997): Nicotine induces long-lasting potentiation in the dentate gyrus of nicotine-primed rats. *Neurosci Res* 29:81–85.
- Hatsukami D, Fletcher L, Morgan S, Keenan R, Amble P (1989): The effects of varying cigarette deprivation duration on cognitive and performance tasks. *J Subst Abuse* 1:407–416.
- Heishman SJ, Taylor RC, Hennigfiels JE (1994): Nicotine and smoking: A review of effects on human performance. *Exp Clin Psychopharmacol* 2:1–51.
- Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA (1996): Prevalence of smoking among psychiatric outpatients. *Am J Psychiatry* 143:993–997.
- Jarrard LE (1995): What does the hippocampus really do? *Behav Brain Res* 71:1–10.
- Jones GMM, Sahakian BJ, Levy R, Warburton DM, Gray JA (1992): Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. *Psychopharmacology* 108:485–494.
- Kellar KJ, Wonnacott S (1990): Nicotinic cholinergic receptors in Alzheimer's disease. In: Wonnacott S, Russell MAH, Stolerman IP, editors. *Nicotine Psychopharmacology: Molecular, Cellular, and Behavioral Aspects*. Oxford, UK: Oxford University Press, 341–373.
- Kim J, Levin E (1996): Nicotinic, muscarinic and dopaminergic actions in the ventral hippocampus and the nucleus accumbens: Effects on spatial working memory in rats. *Brain Res* 725:231–240.
- Leonard S, Adams C, Breese CR, Adler LE, Bickford P, Byerley W, et al (1996): Nicotinic receptor function in schizophrenia. *Schizophr Bull* 22:431–445.
- Levin ED (1992): Nicotine systems and cognitive function. *Psychopharmacology* 108:418–431.
- Levin ED, Bettgowda C, Gordon J, Blosser J (1998a): AR-R 17779, an $\alpha 7$ nicotinic agonist improves learning and memory in rats. *Soc Neurosci Abstr* 24:183.
- Levin ED, Briggs SJ, Christopher NC, Rose JE (1993a): Chronic nicotinic stimulation and blockade effects on working memory. *Behav Pharmacol* 4:179–182.
- Levin ED, Christopher NC, Briggs SJ (1997a): Chronic nicotinic agonist and antagonist effects on T-maze alternation. *Physiol Behav* 61:863–866.
- Levin ED, Christopher NC, Briggs SJ, Auman JT (1996a): Chronic nicotine-induced improvement of spatial working memory and D2 dopamine effects in rats. *Drug Dev Res* 39:29–35.
- Levin ED, Christopher NC, Briggs SJ, Rose JE (1993b): Chronic nicotine reverses working memory deficits caused by lesions of the fimbria or medial basalocortical projection. *Brain Res Cogn Brain Res* 1:137–143.
- Levin ED, Christopher NC, Weaver T, Moore J, Brucato F (1999a): Ventral hippocampal ibotenic acid lesions block chronic nicotine-induced spatial working memory improvement in rats. *Brain Res Cogn Brain Res* 7:405–410.
- Levin ED, Connors CK, Silva D, Hinton SC, Meck WH, March J, Rose JE (1998b): Transdermal nicotine effects on attention. *Psychopharmacology* 140:135–141.
- Levin ED, Connors CK, Sparrow E, Hinton SC, Erhardt D, Meck WH, et al (1996b): Nicotine effects on adults with attention-deficit/hyperactivity disorder. *Psychopharmacology* 123:55–63.
- Levin ED, Damaj MI, Glassco W, May EL, Martin BR (1999b): Bridged nicotine, isonicotine, and norisonicotine effects on working memory performance of rats in the radial-arm maze. *Drug Dev Res* 46:107–111.
- Levin ED, Kaplan S, Boardman A (1997b): Acute nicotine interactions with nicotinic and muscarinic antagonists: Working and reference memory effects in the 16-arm radial maze. *Behav Pharmacol* 8:236–242.
- Levin ED, Kim P, Meray R (1996c): Chronic nicotine effects on working and reference memory in the 16-arm radial maze: Interactions with D1 agonist and antagonist drugs. *Psychopharmacology* 127:25–30.
- Levin ED, Lee C, Rose JE, Reyes A, Ellison G, Jarvik M, Gritz E (1990): Chronic nicotine and withdrawal effects on radial-arm maze performance in rats. *Behav Neural Biol* 53:269–276.
- Levin ED, Rezvani AH (2000): Development of nicotinic drug therapy for cognitive disorders. *Eur J Pharmacol* 393:141–146.

- Levin ED, Rose JE (1990): Anticholinergic sensitivity following chronic nicotine administration as measured by radial-arm maze performance in rats. *Behav Pharmacol* 1:511–520.
- Levin ED, Rose JE, Abood L (1995): Effects of nicotinic dimethylaminoethyl esters on working memory performance of rats in the radial-arm maze. *Pharmacol Biochem Behav* 51:369–373.
- Levin ED, Simon BB (1998): Nicotinic acetylcholine involvement in cognitive function in animals. *Psychopharmacology* 138:217–230.
- Levin ED, Simon BB, Conners CK (2000): Nicotine effects and attention deficit disorder. In: Piasecki M, Newhouse P, editors. *Nicotine in Psychiatry: Psychopathology and Emerging Therapeutics*. Washington, DC: American Psychiatric Society Press, 203–214.
- Levin ED, Toll K, Chang G, Christopher NC, Briggs SJ (1996d): Epibatidine, a potent nicotinic agonist: Effects on learning and memory in the radial-arm maze. *Med Chem Res* 6:543–554.
- Levin ED, Torry D (1995): Nicotine effects on memory performance. In: Clarke PBS, Quik M, Thureau K, Adlkofer F, editors. *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*. Boston: Birkhäuser, 329–336.
- Levin ED, Torry D (1996): Acute and chronic nicotine effects on working memory in aged rats. *Psychopharmacology* 123:88–97.
- Levin ED, Wilson W, Rose J, McEvoy J (1996e): Nicotine-haloperidol interactions and cognitive performance in schizophrenics. *Neuropsychopharmacology* 15:429–436.
- Martin BR, Aceto MD (1981): Nicotine binding sites and their localization in the central nervous system. *Neurosci Biobehav Rev* 5:473–478.
- Muir JL, Everitt BJ, Robbins TW (1995): Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT₃ receptor antagonist, ondansetron. *Psychopharmacology* 118:82–92.
- Newhouse PA, Potter A, Levin ED (1997): Nicotinic system involvement in Alzheimer's and Parkinson's diseases: Implications for therapeutics. *Drugs Aging* 11:206–228.
- Newhouse PA, Sunderland T, Tariot PN, Blumhardt CL, Weingaertner H, Mellow A, Murphy DL (1988): Intravenous nicotine in Alzheimer's disease: A pilot study. *Psychopharmacology* 95:171–175.
- Nordberg A (1993): Clinical studies in Alzheimer patients with positron emission tomography. *Behav Brain Res* 57:215–224.
- Nordberg A (1995): Imaging of nicotinic receptors in human brain. In: Domino EF, editor. *Brain Imaging of Nicotine and Tobacco Smoking*. Ann Arbor, MI: NPP Books, 45–57.
- Nordberg A, Adem A, Hardy J, Winblad B (1988): Change in nicotinic receptor subtypes in temporal cortex of Alzheimer brains. *Neurosci Lett* 88:317–321.
- Ohno M, Yamamoto T, Watanabe S (1993): Blockade of hippocampal nicotinic receptors impairs working memory but not reference memory in rats. *Pharmacol Biochem Behav* 45:89–93.
- Pacheco G, Palacios-Esquivel R, Moss DE (1995): Cholinesterase inhibitors proposed for treating dementia in Alzheimer's Disease: Selectivity toward human brain acetylcholinesterase compared with butyrylcholinesterase. *J Pharmacol Exp Ther* 274:767–770.
- Parks RW, Becker RE, Rippey RF, Gilbert DC, Matthews JR, Kabatay E, et al (1996): Increased regional cerebral glucose metabolism and semantic memory performance in Alzheimer's disease: A pilot double blind transdermal nicotine positron emission tomography study. *Neuropsychol Rev* 6:61–79.
- Perry EK, Perry RH, Smith CJ, Dick DJ, Candy JM, Edwardson JA, et al (1987): Nicotinic receptor abnormalities in Alzheimer's and Parkinson's diseases. *J Neurol Neurosurg Psychiatry* 50:806–809.
- Quirion R, Martel JC, Robitaille Y, Etienne P, Wood P, Nair NP, Gauthier S (1986): Neurotransmitter and receptor deficits in senile dementia of the Alzheimer's type. *Can J Neurol Sci* 13:503–510.
- Raskind MA, Peskind ER, Wessel T, Yuan W (2000): Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology* 54:2261–2268.
- Ridley RM, Murray TK, Johnson JA, Baker HF (1986): Learning impairment following lesion of basal nucleus of Meynert in the marmoset: Modification by cholinergic drugs. *Brain Res* 376:108–116.
- Rinne JO, Myllykylä T, Lönnberg P, Marjamäki P (1991): A postmortem study of brain nicotinic receptors in Parkinson's and Alzheimer's disease. *Brain Res* 547:167–170.
- Rochford J, Sen AP, Quirion R (1996): Effect of nicotine and nicotinic receptor agonists on latent inhibition in the rat. *J Pharmacol Exp Ther* 277:1267–1275.
- Rusted J, Graupner L, Tennant A, Warburton D (1998): Effortful processing is a requirement for nicotine-induced improvement in memory. *Psychopharmacology* 138:362–365.
- Rusted J, Graupner L, Warburton D (1995): Effects of post-trial administration of nicotine on human memory: Evaluating the conditions for improving memory. *Psychopharmacology* 119:405–413.
- Sahakian BJ, Jones GMM (1991): The effects of nicotine on attention, information processing, and working memory in patients with dementia of the Alzheimer type. In: Adlkofer F, Thureau K, editors. *Effects of Nicotine on Biological Systems*. Basel, Switzerland: Birkhauser Verlag, 623–230.
- Salomon AR, Marcinowski KJ, Zagorski M (1996): Nicotine inhibits amyloid formation by the beta-peptide. *Biochemistry* 35:13568–13578.
- Samuels SC, Davis KL (1998): Experimental approaches to cognitive disturbance in Alzheimer's disease. *Harv Rev Psychiatry* 6:11–22.
- Sasaki H, Yanai M, Meguro K, Sekizawa K, Ikarashi Y, Maruyama Y, et al (1991): Nicotine improves cognitive disturbance in rodents fed with a choline-deficient diet. *Pharmacol Biochem Behav* 38:921–925.
- Schroder H, Giacobini E, Wevers A, Birtsch A, Schutz U (1995): Nicotinic receptors in Alzheimer's disease. In: Domino EF, editor. *Brain Imaging of Nicotine and Tobacco Smoking*. Ann Arbor, MI: NPP Books, 73–93.
- Schwartz RD (1986): Autoradiographic distribution of high affinity muscarinic and nicotinic cholinergic receptors labeled with [3H] acetylcholine in rat brain. *Life Sci* 38:2111–2119.

- Shimohama S, Taniguchi T, Fujiwara M, Kameyama M (1986): Changes in nicotinic and muscarinic receptors in Alzheimer-type dementia. *J Neurochem* 46:288–293.
- Snaed J, Johannesson T, Jonsson JE, Gylfadottir G (1996): The effects of nicotine in dermal plaster on cognitive functions in patients with Alzheimer's disease. *Dementia* 7:47–52.
- Socci DJ, Sanberg PR, Arendash GW (1995): Nicotine enhances Morris water maze performance of young and aged rats. *Neurobiol Aging* 16:857–860.
- Stancampiano R, Cocco S, Cugusi C, Sarais L, Fadda F (1999): Serotonin and acetylcholine release response in the rat hippocampus during a spatial memory task. *Neuroscience* 89:1135–1143.
- Standaert D, Young A (1996): Treatment of central nervous system degenerative disorders. In: Hardman JG, Limbird LL, Molinoff PB, Ruddon RW, Gilman AG, editors. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*, 9th ed. New York: McGraw-Hill, 503–519.
- Sugaya K, Giacobini E, Chiappinelli VA (1990): Nicotinic acetylcholine receptor subtypes in human frontal cortex: Changes in Alzheimer's disease. *J Neurosci Res* 27:349–359.
- Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C (2000): A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology* 54:2269–2276.
- Terry AV, Buccafusco JJ, Decker MW (1997): Cholinergic channel activator, ABT-418, enhances delayed-response accuracy in rats. *Drug Dev Res* 40:304–312.
- Terry AV, Buccafusco JJ, Jackson WJ, Zagrodnik S, Evansmartin FF, Decker MW (1996): Effects of stimulation or blockade of central nicotinic-cholinergic receptors on performance of a novel version of the rat stimulus discrimination task. *Psychopharmacology* 123:172–181.
- Warburton D, Mancuso G (1998): Evaluation of the information processing and mood effects of a transdermal nicotine patch. *Psychopharmacology* 135:305–310.
- Warburton DM, Arnall C (1994): Improvements in performance without nicotine withdrawal. *Psychopharmacology* 115:539–542.
- White HK, Levin ED (1999): Four week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. *Psychopharmacology* 143:158–165.
- Wilens TE, Biederman J, Spencer TJ, Bostic J, Prince J, Monuteaux MC, et al (1999): A pilot controlled clinical trial of ABT-418, a cholinergic agonist, in the treatment of adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 156:1931–1937.
- Williams DG (1980): Effects of cigarette smoking on immediate memory and performance in different kinds of smoker. *Br J Psychol* 71:83–90.
- Wilson AL, Langley LK, Monley J, Bauer T, Rottunda S, Mcfalls E, et al (1995): Nicotine patches in Alzheimer's disease: Pilot study on learning, memory, and safety. *Pharmacol Biochem Behav* 51:509–514.
- Wonnacott S (1997): Presynaptic nicotinic ACh receptors. *Trends Neurosci* 20:92–98.
- Wonnacott S, Irons J, Rapier C, Thorne B, Lunt GG (1989): Presynaptic modulation of transmitter release by nicotinic receptors. *Prog Brain Res* 79:157–163.
- Zarrindast MR, Sadegh M, Shafaghi B (1996): Effects of nicotine on memory retrieval in mice. *Eur J Pharmacol* 295:1–6.