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REVIEW

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Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization

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Abstract *Rationale:* Nicotine has been shown in a variety of studies in humans and experimental animals to improve cognitive function. Nicotinic treatments are being developed as therapeutic treatments for cognitive dysfunction. *Objectives:* Critical for the development of nicotinic therapeutics is an understanding of the neurobehavioral bases for nicotinic involvement in cognitive function. *Methods:* Specific and diverse cognitive functions affected by nicotinic treatments are reviewed, including attention, learning, and memory. The neural substrates for these behavioral actions involve the identification of the critical pharmacologic receptor targets, in particular brain locations, and how those incipient targets integrate with broader neural systems involved with cognitive function. *Results:* Nicotine and nicotinic agonists can improve working memory function, learning, and attention. Both $\alpha 4\beta 2$ and $\alpha 7$ nicotinic receptors appear to be critical for memory function. The hippocampus and the amygdala in particular have been found to be important for memory, with decreased nicotinic activity in these areas impairing memory. Nicotine and nicotinic analogs have shown promise for inducing cognitive improvement. Positive therapeutic effects have been seen in initial studies with a variety of cognitive dysfunctions, including Alzheimer's disease, age-associated memory impairment, schizophrenia, and attention deficit hyperactivity disorder. *Conclusions:* Discovery of the behavioral, pharmacological, and anatomic specificity of nicotinic effects on learning, memory, and attention not only aids the understanding of nicotinic involvement in the basis of cognitive function, but also helps in the development of novel nicotinic treatments for cognitive dysfunction. Nicotinic treatments directed at specific receptor subtypes and nicotinic cotreatments with drugs affecting interacting transmitter systems may provide cognitive benefits most relevant to different syndromes of cognitive impairment such as Alzheimer's disease, schizophrenia, and attention deficit hyperactivity disorder. Further research is necessary in order to determine the efficacy and safety of nicotinic treatments of these cognitive disorders.

Keywords Nicotine · Attention · Learning · Memory · Hippocampus · Amygdala · Alzheimer's disease · Schizophrenia · ADHD

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Introduction

Nicotine, a tertiary amine compound, has long been known to be the primary psychoactive agent in tobacco smoke. Early research on the effects of nicotine and smoking on cognitive performance largely confirmed smoker reports, showing abstinence to disturb and smoking/nicotine administration to restore cognitive functioning (Heishman et al. 1994). However, because the majority of these studies examined the effects of nicotine on nicotine-deprived smokers, they could not provide conclusive evidence regarding the absolute effects of nicotine on information processing.

More recently, research using human nonsmokers and experimental animals has provided a clearer picture of the effects of nicotine on cognitive processes. This research has been spurred on by efforts to better understand (1) the neurochemical basis of cognitive systems and functions with known nicotinic receptor involvement and (2) psychiatric problems thought to have disturbances of cholinergic systems as part of their pathogenesis. In this review, we examine the behavioral, neurochemical, anatomical, and clinical bases of nicotine and nicotinic modulation on cognitive function.

Behavioral characterization

Learning and memory

Involvement of neuronal nicotinic cholinergic systems in learning and memory processes has been recognized for

several decades (Levin 1992, 2000a; Rezvani and Levin 2001; Stolerman et al. 1995). Cognitive improvement induced by nicotine and nicotinic agonists has been documented in humans and a variety of animal models (Table 1).

Animal studies

An intriguing association between neuronal nicotinic systems and learning and memory is evident from numerous studies in humans, primates, rodents, zebrafish, and other laboratory animals. Nicotine administration has been shown to improve learning and memory in different test procedures (Levin 1999, 2000a, 2002; Levin et al. 2004b; Puma et al. 1999; Rezvani and Levin 2001; Yilmaz et al. 1997). Below is a brief summary of recent findings on the effects of nicotine and nicotine agonists on learning and memory functions using different tasks.

Both acute and chronic nicotine treatments have been shown using the radial-arm maze to significantly improve working memory function in rats. The eight-arm maze is a standard test and a sensitive measure of working memory performance (Levin 2000b). Working memory is defined as memory with changing contents, as opposed to reference memory, which is defined as memory with fixed contents (Decker et al. 1995; Levin and Simon 1998). Levin et al. (1997) have shown in several studies that a single dose of 0.2 mg kg^{-1} nicotine ditartrate salt injected subcutaneously 20 min before testing significantly improved working memory in female rats. Other selective nicotinic agonists such as dimethylaminoethanol (Levin et al. 1995), epibatidine (Levin et al. 1996d), ARR 17779 (Levin et al. 1999a), ABT-418 (Decker et al. 1994), TC-1734 (Gatto et al. 2004), and lobeline (Levin and Christopher 2003; Rochford et al. 1996; Terry et al. 1996) also have been found to improve learning and memory. Important for possible clinical use, it has been shown in animals that the efficacy of nicotine-induced improvement of memory does not diminish with chronic administration. We have seen continuing improvement of radial-arm maze working memory performance with chronic nicotine infusion over several weeks at a time (Levin et al. 1990a, 1992, 1993a,b). Chronic treatment with nicotine agonists has also been shown to improve memory performance in other memory tasks, such as one-way avoidance and Lashley III maze (Arendash et al. 1995a). Similarly, it has been demonstrated using a passive avoidance task that the immediate posttraining systemic administration of nicotine enhances retention in a dose-dependent manner in CD1 mice (Ciamei et al. 2001).

Improvements in memory by nicotinic agonists likely extend to a wide range of vertebrates (Levin and Chen 2004). As in rodents, low doses of nicotine also improve memory function in zebrafish, while high doses can impair memory. Nicotine was administered by placing the fish in a beaker containing 50 ml of tank water mixed with 50–800 mg l^{-1} of nicotine ditartrate for 30 min, and memory function was tested using delayed spatial alteration. Recently, it has been shown in zebrafish that nicotine also significantly improves choice accuracy on a rapid single-session spatial discrimination task (Levin et al. 2005b).

In addition to spatial memory tasks, another task for assessing working memory is the object recognition working memory task. It has been reported that rats are able to discriminate between a familiar object and a new object for 1 h or less after initial presentation of the familiar object, but not 24 h after the presentation (Puma et al. 1999). Acute nicotine administration enhanced acquisition, consolidation, and restitution of the information in an object recognition task in rats (Puma et al. 1999). These findings are similar to other findings showing that nicotine improves spatial working memory in rats (Levin et al. 1996c), demonstrating some generality of the effect of nicotine on cognitive function.

The eye-blink classical conditioning procedure is an extensively used measure of associative learning and memory. Both in human and rabbit, the involvement of the cholinergic system in eye-blink conditioning has been demonstrated (Woodruff-Pak et al. 2000). Recently, it has been demonstrated that nicotine and GTS-21 (a selective $\alpha 7$ nicotinic receptor partial agonist that antagonizes $\alpha 4\beta 2$ nicotinic receptors) can reverse mecamylamine-induced deficits in eye-blink conditioning in rabbits. These findings support the notion that nicotinic agonists may have efficacy in ameliorating learning associated with cholinergic deficits.

Studies evaluating the effects of nicotine on memory and learning in young vs old animals provide a mixed picture of age-related effects. An assessment of the effects of nicotine on learning and memory in young and senescent Fisher 344 rats has shown that, in young rats, nicotine (0.2 mg kg^{-1}) improved the acquisition of a serial pattern in the Morris water maze procedure, suggesting an improvement in working memory. No beneficial effects of nicotine in reference memory were found in either age group (Attaway et al. 1999). The authors argue that nicotine may not be beneficial in attenuating age-related learning and memory deficits. Although their data support this notion, only one dose of nicotine in an acute form was tested in this study. Thus, this study should be considered inconclusive. In contrast with these findings, nicotine and nicotinic agonist ABT-418 have been shown to improve memory in both young (Buccafusco and Jackson 1991; Buccafusco et al. 1995; Elrod et al. 1988; Jackson et al. 1989; Rupniak and Iversen 1989) and aged monkeys (Buccafusco and Jackson 1991; Jackson et al. 1989) and in senescence-accelerated mice (Meguro et al. 1994) and aged rats (Levin and Torry 1996; Socci et al. 1995). However, chronic nicotine administration fails to improve working memory in aged rats, possibly due to the decrease in functional nicotinic receptors in aged animals (Levin and Torry 1996).

Nicotine has not been uniformly found to improve cognitive function. For example, it has been shown that chronic administration of nicotine (0.35 mg kg^{-1} for 10 days) in NMRI male mice did not significantly change performance in the water maze at any age tested (Vicens et al. 2003). Moragrega et al. (2003) also have reported that acute administration of nicotine (0.35 and 0.175 mg kg^{-1})

Table 1 Effects of nicotine, nicotine agonists, and antagonists on learning and memory and attention in different species

Compounds	Species	Task	Effects	References
Learning and memory				
Nicotine	Rats	Radial-arm maze	+	Levin 1992, 2000a, 2002; Levin and Chen 2004
Nicotine	Rats	Object recognition	+	Puma et al. 1999
Nicotine	Mice	Passive avoidance	+	Ciamei et al. 2001
Nicotine	Rats	Acquisition of serial pattern	No effect	Attaway et al. 1999
Nicotine	Rats (aged)	Water maze	+	Socci et al. 1995
Nicotine	Rats (aged)	Radial-arm maze	+	Levin and Torry 1996
Nicotine	Fisher rats (aged)	Water maze	+	Attaway et al. 1999
Nicotine chronic	Rats (young)	Radial-arm maze	+	Levin and Torry 1996
Nicotine chronic	Rats (aged)	Radial-arm maze	No effect	Levin and Torry 1996
Nicotine chronic	Mice	Water maze	No effect	Vicens et al. 2003
Nicotine	Mice (aged)	Passive avoidance	+	Meguro et al. 1994
Nicotine	Mice	5-CSR	+	Young et al. 2004
Nicotine	Mice	Water maze	−	Moragrega et al. 2003
Nicotine	Zebrafish	Spatial alternation	+	Levin and Chen 2004
Nicotine	Rabbits	Eye-blink conditioning	+	Woodruff-Pak et al. 2000
Nicotine	Monkeys (aged)	Delayed matching-to-sample	+	Jackson et al. 1989; Buccafusco and Jackson 1991
Nicotine	Human (smokers and nonsmokers)	Memory	+	McClernon et al. (2003)
Dimethylaminethanol	Rats	Radial-arm maze	+	Levin et al. 1995, 1996d
Epibatidine	Rats	Radial-arm maze	+	Levin et al. 1999a
AAR-17779	Rats	Radial-arm maze	+	Levin et al. 1999a
ABT-418	Rats	Radial-arm maze	+	Decker et al. 1994
TC-1734	Rats	Radial-arm maze	+	Gatto et al. 2004
TC-1734	Mice	Object recognition	+	Gatto et al. 2004
Lobeline	Rats	Latent inhibition	+	Rochford et al. 1996; Terry et al. 1996
Lobeline	Rats	Radial-arm maze	+	Levin and Christopher 2003
Mecamylamine	Rats	Radial-arm maze	−	Levin and Torry 1996
DHβE	Rats	Radial-arm maze	−	Felix and Levin 1997
MLA	Rats	Radial-arm maze	−	Levin et al. 2000
GTS-21	Rabbits	Eye blink	+	Woodruff-Pak et al. 2000
ABT-418	Monkeys (young)	Delay matching-to-sample	+	Buccafusco et al. 1995
Attention				
Nicotine	Rats	Visual signal detection	+	Rezvani et al. 2002, 2004
Nicotine	Rats	5-CSR	+	Mirza and Stolerman 1998; Muir et al. 1995; Stolerman et al. 2000; Bizzaro and Stolerman 2003
ABT-418	Rats	Visual signal detection	+	McGaughy et al. 1999
Nicotine	Rats	5-CSR	No effect	Mirza and Bright 2001
SIB-1553A	Rats	5-CSR	+	Terry et al. 2002
Mecamylamine	Rats	5-CSR	−	Grottick and Higgins 2000; Mirza and Stolerman 1998
Mecamylamine	Rats	Visual signal detection	−	Rezvani et al. 2002
Nicotine	Nonsmokers	Attention	+	Levin et al. 2000
Nicotine	Human	Visual information-processing	+	Lawrence et al. 2002

+ indicates improvement in performance; − indicates impairment in performance

did not improve acquisition in the water maze in group-housed mice and even impaired it in individually housed mice.

While as reviewed above, nicotinic agents have been shown to improve memory in normal rats, there is growing evidence that these agents can lead to improvement in laboratory models of memory and learning impairment. For instance, there is evidence that nicotine can counteract memory deficits induced by lesions of the forebrain cholinergic projection systems in a passive avoidance task, water maze task, or radial maze task (Decker and Majchrzak 1992; Decker et al. 1992; Grigoryan et al. 1994; Hodges et al. 1991; Riekkinen et al. 1993). Chronic nicotine infusion also has been shown to reverse working memory deficits due to lesions of fimbria medial basalocortical projection (Levin et al. 1993b).

Nicotine has been found to attenuate learning impairments caused by AF64A in rats. AF64A is a neurotoxic derivative of choline that produces long-lasting cholinergic deficits. Administration of this neurotoxin into the hippocampus has been shown to deplete acetylcholine in this region and impair memory function (Hiramatsu et al. 2002). Repeated administration of nicotine reduced learning and memory impairments in the passive avoidance test caused by AF64A. However, acute injection of nicotine did not improve the AF64A-induced impairment in learning and memory. Interestingly, although repeated administration of nicotine improved the cognitive impairments caused by AF64A, it did not change choline acetyltransferase activity in the hippocampus of AF64A-treated rats. The orally effective nicotinic agonist TC-1734 significantly attenuates deficits in passive avoidance caused by the muscarinic cholinergic antagonist scopolamine (Gatto et al. 2004).

Long-term potentiation (LTP) in the hippocampus CA1 regions is regarded to be the cellular substrate of learning and memory. Recently, it has been shown that cholinergic lesions by cholinergic toxic 192-IgG-saporin infused into the lateral cerebral ventricle impaired the induction of LTP in hippocampal slices. Nicotine has been shown to reverse this effect and promote the induction of LTP (Yamazaki et al. 2002).

Developmentally lead-exposed animals exhibit significant deficits in spatial reference memory acquisition and working memory performance in the Morris water maze. Zhou and Suskiw (2004) have demonstrated that acute systemic administration of nicotine reversed these deficits in rats.

Finally, it has been demonstrated that pretrial nicotine administration attenuates the impairment in working and reference memory function induced by MK-801 (dizocilpine) in rats (Levin et al. 1998), suggesting a functional interaction between nicotinic and glutamatergic systems in the brain (see "Interactions with other transmitter receptor systems").

Human studies

Very few studies have evaluated the effects of nicotine on memory performance among normal nonsmokers. In a double-blind, placebo-controlled study, McClernon et al. (2003) observed nicotine to decrease working memory errors in both smokers (14 or 21 mg) and nonsmokers (7 mg), but only when distracting stimuli were presented in the right visual field during rehearsal. Distractors presented in the left visual field worsened performance in the nicotine condition. These findings suggest nicotine may enhance working memory by decreasing distractability and that nicotine's effects on cognition may be lateralized.

Attention

Although the effects of nicotine and its agonists on learning and memory have been studied extensively, their effects on attention have been far less investigated. However, there is enough evidence to suggest that, in addition to improving learning and memory (Rezvani and Levin 2001), the stimulation of nicotinic receptors by nicotine can provide some improvement of attentional functions both in animals and humans.

Animal studies

Although memory improvement with nicotine is more clearly seen in rodents than the improving effects of nicotine on other cognitive functions, there is enough evidence to confirm that nicotine can also improve attention in experimental animals (Grilly 2000; Mirza and Bright 2001; Mirza and Stolerman 1998; Muir et al. 1995; Rezvani et al. 2002; Rezvani and Levin 2003a; Stolerman et al. 2000). Using an operant visual signal detection task, it has been demonstrated that a low-dose range of nicotine (0.0125–0.05 mg kg^{-1}) caused an increase in percent correct rejection, suggesting an improvement in attention as reflected in an increase in choice accuracy (Rezvani et al. 2002; Rezvani and Levin 2003a,b). In the same procedure, the nicotinic antagonist mecamylamine decreased choice accuracy by reducing both percent hit and percent correct rejection (Rezvani et al. 2002).

The five-choice serial reaction time task (5-CSRTT) is a well-validated rodent model of attention that requires the detection of a signal light presented randomly in one of five locations during 30-min sessions (Robbins 2002). Mecamylamine has been shown to impair performance in this task, as it did in the operant signal detection task (Grottick and Higgins 2000; Mirza and Stolerman 1998). Using the same task, Ruotsalainen et al. (2000) only reported a decrement in reaction time, not accuracy, following mecamylamine challenge in rats. The cognitive impairing effects of mecamylamine suggest the involvement of the neuronal nicotinic cholinergic system in normal cognitive functioning. Nicotine agonist ABT-418 has also been shown to improve accuracy in the operant signal detection task (McGaughy et al. 1999).

Nicotine-induced enhancement in performance in attention has been shown to be strain-dependent. Mirza and Bright (2001) showed that nicotine treatment improved

attention in the 5-CSRTT in Sprague–Dawley rats, which have lower baseline performance, but not in Lister hooded rats. These findings suggest that there may be critical strain-related differences in nicotinic receptors or neural systems related to the expression of nicotinic receptors important for cognitive function as much as there is with nicotine reinforcement (Shoaib et al. 1997).

Nicotinic analog treatment has also been shown to improve attention. Terry et al. (2002) found that the nicotinic agonist SIB-1553A significantly improves performance of rats on a five-choice attentional task, but only when accuracy was reduced behaviorally with a distracting stimulus or pharmacologically by injecting the rats with the NMDA-sensitive glutamate receptor antagonist dizocilpine (MK-801).

Nicotine has also been shown to reverse attentional impairments in rats caused by basal forebrain lesions (Mirza and Stolerman 1998; Muir et al. 1995; Stolerman et al. 2000) or lesions of the septohippocampal pathways (Levin et al. 1993b). Interestingly, chronic nicotine infusion has been shown to significantly diminish the impairing effects of the typical antipsychotic drug haloperidol (Rezvani et al. 2004) and atypical antipsychotic drugs clozapine and risperidone (Rezvani et al. 2004) on attentional performance in rats using an operant visual signal detection task.

Nicotine, but not amphetamine, increased accuracy and the number of trials completed, suggesting that psychomotor stimulant properties shared by these two drugs were not solely responsible for their effects on attentional performance on the 5-CSRTT (Bizzaro and Stolerman 2003).

Human studies

The issue concerning whether nicotine can improve attentiveness in normal nonsmokers who have no preexisting attentional impairment has been addressed. Adult nonsmokers without attention deficit hyperactivity disorder (ADHD) symptoms were administered either 7 mg kg^{-1} day^{-1} nicotine patches or placebo for 4.5 h day^{-1}. It was found that the administration of nicotine significantly reduced the number of errors of omission on the continuous performance task (CPT). No change in errors of commission was found. It was also found that the nicotine patch significantly decreased response time variability and increased a composite attention measure. Overall, this study demonstrated that nicotine given transdermally could improve attention in nonsmoking subjects who had no preexisting attentional deficits (Levin et al. 2000).

Selective effects of nicotine on attentional processes have also been studied in smokers. Smokers who abstained from smoking for at least 10 h prior to testing were treated with 21 mg nicotine transdermal patches for either 3 or 6 h and tested for selective effects of nicotine on attention using the Random Letter Generation test, the Flexibility of Attention test, and the Stroop test. It was shown that the 6 hr, but not the 3 h, nicotine patch enhanced the speed of number generation and the speed of processing in both the control and interference condition of the Stroop test. There were no effects on attentional switching of the Flexibility of Attention test. The authors suggest that nicotine mainly improves the intensity features of attention, rather than the selectivity features (Mancuso et al. 1999). The nicotinic agonist ABT-418 was found to improve symptoms of ADHD in adults with the syndrome (Wilens et al. 1999). Nicotine-induced attentional improvement has been found in MRI imaging studies to be accompanied by increased activation in the parietal cortex, thalamus, and caudate (Lawrence et al. 2002). Kumari et al. (2003) found that nicotine-induced improvements in an n-back memory task were accompanied by increases in activity in several cortical regions of interest, the anterior cingulate cortex, the superior frontal cortex, and the superior parietal cortex, during n-back task performance.

Pharmacological specification

Nicotinic receptor subtypes

Nicotinic receptors constitute a family of ligand-gated ion channels (Changeux 1990a,b) that include a variety of receptor subtypes, which, as reviewed above, are important for a variety of neurobehavioral functions including cognitive function (Changeux et al. 1998). The development of novel nicotinic ligands for the treatment of cognitive deficits depends on determining the differential roles of various nicotinic receptor subtypes. Putatively, receptor subtype selectivity is a primary means of achieving greater clinical efficacy with fewer side effects. Effects of systemic application of nicotinic receptor subtype ligands are described below, with the brain-region-specific local infusion data presented in the later section on anatomic localization.

Nicotinic α4β2 receptors

Nicotinic α4β2 receptors have been shown to be critically involved in cognitive function. Nicotinic agonists of α4β2 receptors such as RJR 2403 (Papke et al. 2000) produce significant improvement in memory function (Levin and Christopher 2002; Lippiello et al. 1996). Interestingly, the memory improvement caused by RJR 2403 was long-lasting, with significant improvement seen 6 h after acute administration, long past the half-life of the drug (Levin and Christopher 2002). The α4β2 agonist SIB 1765F significantly improves attentional accuracy in the five-choice task (Grottick and Higgins 2000).

Nicotinic α7 receptors

Nicotinic α7 receptors have not classically been thought to be involved in cognitive function, although recent data point to the importance of these receptors. The α7 agonist ARR 17779 significantly improved learning and memory

in rats (Levin et al. 1999a). Van Kampen et al. (2004) found that this α7 agonist significantly improved social recognition in rats. Some investigators did not find ARR 17779 to effectively improve choice accuracy in the five-choice task (Grottick and Higgins 2000; Hahn et al. 2003). However, Young et al. (2004) found that α7 knockout mice had significant impairments on the five-choice task. The partial α7 agonist GTS 21 significantly improved learning and memory (Arendash et al. 1995b) and also attenuated the age-related impairment of classical conditioning in rabbits (Woodruff-Pak et al. 2000). The involvement of nicotinic α7 receptors in specific brain regions such as the ventral hippocampus with memory function is discussed below in the anatomy section.

Other nicotinic receptors

Nicotinic receptors other than α7 and α4β2 certainly exist in the brain. The involvement of α3- and α6-containing and other nicotinic receptors in cognitive function remains to be determined. This is in a large part due to the lack of specific agonists and antagonists for these other receptors. Once this deficit in adequate pharmacologic tools is remedied, progress can be made in the understanding of other nicotinic receptor subtype involvement in cognitive function.

Interactions with other transmitter receptor systems

Clearly, no transmitter system in the brain functions in isolation with respect to cognitive function—the brain is an organ of integration. This is particularly true for a complex function like memory, where nicotinic ACh receptors play a critical role (Bartus et al. 1987; Brioni et al. 1997; Decker et al. 1995; Levin 1992; Levin and Simon 1998; Warburton 1992). However, nicotinic systems interact with a variety of other neurotransmitter systems with regard to cognitive function (Decker and McGaugh 1991; Levin and Simon 1998) as nicotine promotes the release of several neurotransmitters important for cognitive function including acetylcholine, dopamine (DA), serotonin, gamma-aminobutyric acid (GABA), and glutamate (Wonnacott et al. 1989).

Muscarinic acetylcholine receptors

Muscarinic acetylcholinergic receptors, the other main type of acetylcholine receptors, have long been known to play key roles in cognitive function. Nicotine and other nicotinic agonists can indirectly act as muscarinic agonists by stimulating the release of acetylcholine. The muscarinic antagonist scopolamine is a classic amnestic drug. We have found that the working memory improvement caused by nicotine administration is blocked by scopolamine (Levin and Rose 1991). In addition, scopolamine produces mutually potentiating memory impairments when administered with the nicotinic antagonist mecamylamine (Levin et al. 1989b).

Dopamine

Dopamine systems are critical for a variety of behavioral systems, from motor function to reinforcement and cognitive function. DA blockade was not found to attenuate nicotine-induced memory improvement (Levin 1997). Dopaminergic antagonists such as haloperidol cause memory impairments, which can be attenuated by nicotine (Levin and Rose 1995). Systemic administration of dopamine D1 receptor partial agonist SKF 38393 prior to testing affected aspects of accuracy and vigor of responding in a rodent five-choice reaction time task (Passetti et al. 2003). In addition, when it was infused into the medial prefrontal cortex, SKF38393 increased choice accuracy, particularly in rats with low baseline performance (Granon et al. 2000).

The impairment caused by nicotinic blockade is potentiated by DA blockade with haloperidol (McGurk et al. 1989a). The haloperidol-induced potentiation of the mecamylamine effect seems to be mediated via the D_2 receptor subtype (McGurk et al. 1989b). Supporting the involvement of D_2 mechanisms with nicotinic effects is the finding that the selective D_2 agonist quinpirole reversed the mecamylamine-induced deficit in radial-arm maze choice accuracy (Levin et al. 1989a). The partial D_1 agonist SKF 38393 was not effective. This reversal of the mecamylamine-induced deficit did not seem to be due merely to additivity of choice accuracy effects since quinpirole did not, by itself, improve choice accuracy and had previously been found to impair it (Levin and Bowman 1986). Quinpirole was also found to attenuate the memory deficit caused by combined nicotinic and muscarinic blockade (Levin et al. 1990b), but quinpirole was not effective in reversing the radial-arm maze impairment caused by scopolamine alone (Levin and Rose 1992), supporting the specificity of D_2 interactions with nicotinic systems with regard to memory function. We have found that muscarinic ACh systems have more important interactions with D_1 systems (Levin and Rose 1992).

In addition to reversing mecamylamine-induced memory deficits, we have found that the D_2 agonist quinpirole has additive effects with nicotine in improving memory function (Levin and Eisner 1994). Rats trained to asymptotic performance in the radial-arm maze were given nicotine ditartrate (0.2 mg kg^{-1}) alone or in combination with the D_2 agonist quinpirole (0.05 mg kg^{-1}). There was a significant main effect of nicotine, improving choice accuracy. There was no indication that quinpirole by itself improved choice accuracy. Interestingly, the combination of quinpirole and nicotine did improve performance, over nicotine alone. Quinpirole-induced potentiation of the nicotine effect was expected because quinpirole was found to reverse the memory deficit caused by the nicotinic antagonist mecamylamine.

The DA antagonist haloperidol does not block acute nicotine-induced memory improvement in humans taking haloperidol to treat schizophrenia (Levin et al. 1996e). Specifically, D_2 blockade, either acute or chronic, does not attenuate acute or chronic nicotine-induced memory improvement (Addy and Levin 2002; Levin 1997; Levin et al.

1996a). Nicotine does have significant interactions with D_1 systems. Acute nicotine treatment attenuates the memory impairment caused by D_1 agonist treatment (Levin and Eisner 1994). In contrast, chronic nicotine administration increases the memory impairment caused by the D_1 agonist dihydrexidine and decreases the memory improvement caused by the D_1 antagonist SCH 23390 (Levin et al. 1996c). These relationships may be important clinically in cases when nicotinic and dopaminergic systems are concurrently affected by the disease process and treatment such as in schizophrenia and Parkinson's disease (PD).

Serotonin

Serotonin (5-HT) is critical to a number of nicotinic actions. Systemic administration of ketanserin, a 5-$HT_{2a/c}$ receptor antagonist, significantly reduced premature responding in a model of attention (Passetti et al. 2003). Infusion of ketanserin into the medial prefrontal cortex failed to improve percent correct responses but dose-dependently increased latency. In a subset of animals with relatively high premature response, it reduced premature responses (Passetti et al. 2003). Other serotoninergic receptors might be involved as well. Recently, it was shown that ketanserin administered subcutaneously did not affect the choice performance in a visual signal attention task in rats (Rezvani et al. 2005). However, the same dose of ketanserin when given in combination with nicotine significantly diminished the improving effects of nicotine on attentional performance, suggesting a functional interaction between the nicotinic and serotoninergic systems on sustained attention (Rezvani et al. 2005). In a similar fashion, nicotine-induced improvement of working memory in the radial-arm maze was attenuated with ketanserin administration (Levin et al. 2005a).

Gamma-aminobutyric acid

Gamma-aminobutyric acid is the primary inhibitory neurotransmitter in the brain. The GABA-B antagonist baclofen improves working memory at low doses and impairs working memory at higher doses (Levin et al. 2004b). Concurrent nicotine administration attenuates both the positive low-dose effects and the negative high-dose effects of baclofen on working memory performance (Levin et al. 2004b), suggesting a functional interaction between these two systems.

Glutamate

Glutamate is the primary excitatory neurotransmitter in the brain. Blockade of NMDA glutamate receptors with dizocilpine (MK-801) causes substantial working and reference memory impairment in the radial-arm maze. This is attenuated by concurrent nicotine administration (Levin et al. 1998). The amnestic effects of dizocilpine infusions into the ventral hippocampus were potentiated by concurrent systemic nicotine administration (Levin et al. 2003), an effect that was not seen with dizocilpine infusions in the basolateral amygdala or the piriform cortex (May-Simera and Levin 2003). The reversal of systemic nicotine effects on memory in the radial-arm maze with dizocilpine infusions in the ventral hippocampus suggests that nicotine-induced glutamate release in the hippocampus is critical for systemic nicotine-induced memory improvement.

Other neurotransmitter systems

As mentioned previously, nicotine stimulates the release of a variety of neurotransmitters. Other neurotransmitter systems certainly interact with nicotinic receptor systems in the neural substrate of cognitive function. In particular, norepinepherine and histamine are transmitters that are known to be important for cognitive function, and their release is stimulated by nicotine. Nicotine-induced norepinepherine release in the hippocampus may be important for nicotine-induced memory improvement (Fu et al. 1998; Mitchell et al. 1990). Nicotinic and histaminergic systems appear to play complementary roles in cognitive function (Blandina et al. 2004). Histamine coadministration was found to reduce the improvement in passive avoidance learning by nicotine, whereas histamine antagonists enhanced nicotine-induced improvements (Eidi et al. 2003). Histamine stimulates the activity of cholinergic cells in the septum and basal forebrain, but the interactions of histaminergic and nicotinic systems likely differ substantially according to the receptor subtypes involved (Bacciottini et al. 2001). Histamine H1 and H3 receptors appear to have opposite effects on memory function, with H1 antagonist treatment impairing and H3 antagonist treatment improving function (Chen 2000; Chen et al. 2001).

Anatomic localization

Hippocampus

A large body of literature examines the role of the hippocampus as a key neural component of cognitive function (Jarrard 1995). Local infusion of the nicotinic antagonist mecamylamine into the hippocampus has been shown to cause working memory impairment (Kim and Levin 1996; Ohno et al. 1993). We have conducted a series of studies of the role of nicotinic $\alpha7$ and $\alpha4\beta2$ nicotinic receptors in the ventral hippocampus for working memory (Table 2). Acute infusion of either the $\alpha7$ antagonist MLA or the $\alpha4\beta2$ antagonist DHβE into the ventral hippocampus causes working memory impairment in the radial-arm maze (Bancroft and Levin 2000; Felix and Levin 1997; Levin et al. 2002). Interestingly, it was found that the radial-arm maze memory impairment caused by nicotinic $\alpha4\beta2$ blockade with DHβE in the ventral hippocampus was reversed by chronic systemic nicotine infusion. This suggests that full activation of ventral hippocampal $\alpha4\beta2$

Table 2 Effects of nicotinic antagonists on working memory of rats in the radial-arm maze

Compound	Brain region	Effects	Comments	Reference
Mecamylamine	Ventral hippocampus	Deficit		Kim and Levin 1996
DHβE	Ventral hippocampus	Deficit	Not additive with MLA-induced improvement	Bancroft and Levin 2000; Felix and Levin 1997; Levin et al. 2002
MLA	Ventral hippocampus	Deficit	Not additive with DHβE-induced improvement	Bancroft and Levin 2000; Felix and Levin 1997; Levin et al. 2002
DHβE	Basolateral amygdala	Deficit		Addy et al. 2003
MLA	Basolateral amygdala	Deficit	Reverses DHβE-induced improvement	Addy et al. 2003
DHβE	Frontal cortex	0		Levin et al. 2004a
MLA	Frontal cortex	0		Levin et al. 2004a
Mecamylamine	Ventral tegmental area	Deficit		Levin et al. 1994
Mecamylamine	Substantia nigra	Deficit		Levin et al. 1994
Mecamylamine	Nucleus accumbens	0		Kim and Levin 1996
DHβE	Dorsomedial thalamic nucleus	Improvement		Levin et al. 2004a
MLA	Dorsomedial thalamic nucleus	0	Reverses DHβE-induced improvement	Levin et al. 2004a

is not necessary for the expression of nicotine's memory-improving effects. On the other hand, we have found that chronic systemic nicotine infusion failed to block ventral hippocampal MLA-induced memory impairment on the same radial-arm maze task, suggesting that hippocampal α7 nicotinic receptors in the ventral hippocampus are probably key to nicotine's positive effects on memory function.

The amnestic effect of nicotinic blockade in the ventral hippocampus does not seem to diminish with prolonged antagonist action. Chronic 4-week infusion of DHβE into the ventral hippocampus causes working memory impairment of rats in the radial-arm maze, with no apparent diminution of effect over time (Arthur and Levin 2002).

Lesions within the hippocampus have been found to eliminate nicotinic drug effects on memory. Modest ibotenic lesions in the ventral hippocampus, which in themselves do not impair working memory performance in the radial-arm maze, eliminated the memory improvement with chronic nicotine administration (Levin et al. 1999b). Lesions of the fimbria-fornix, which carries connections between the hippocampus and septum, significantly impair working memory on the radial-arm maze. This effect is reversed by chronic nicotine infusion (Levin et al. 1993b) or repeated injections of the selective nicotinic α7 agonist ARR 17779 (Levin et al. 1999a). Neonatal ventral hippocampal lesions eliminated the amnestic effects of the nicotinic antagonist mecamylamine (Chambers et al. 1996).

Amygdala

The amygdala has classically been thought to be critical for emotional components of cognitive function, but it may play critical roles in nonemotional memory as well (McGaugh et al. 2002). In this regard, we have shown that nicotinic receptor blockade in the amygdala causes memory impairment in an appetitively motivated spatial memory task (Addy et al. 2003). Either MLA or DHβE infusions into the basolateral amygdala impaired working memory performance in the radial-arm maze. This indicates the involvement of both nicotinic α7 and α4β2 receptors of the basolateral amygdala in the functional basis of memory function. Interestingly, despite the finding that either MLA and DHβE given alone in the amygdala caused memory impairments, coadministration of these two compounds caused an amelioration of the deficits caused by either alone (Addy et al. 2003), suggesting that they had separate actions that had mutually attenuating effects on memory function.

Frontal cortex

The frontal cortex has been shown in a variety of studies to be important for cognitive function. The nicotinic receptor subtypes expressed in the frontal cortex have been implicated in attentional performance (Vidal 1996). Local infusion of nicotine into the frontal cortex caused a significant dose-related increase in choice accuracy in a 5-CSRTT (Hahn et al. 2003). We have found that the doses of MLA or DHβE, which effectively impair working memory when infused into the ventral hippocampus, failed to exert an impairing effect on working memory when infused into the medial or lateral frontal cortex (Levin et al. 2004a).

Thalamus

The thalamus is the site of substantial nicotinic receptor concentration (Rubboli et al. 1994). Several areas of the

thalamus have been shown to be important for cognitive function. The mediodorsal thalamic nucleus has reciprocal direct connections with the frontal cortex. Electrolytic lesions of the mediodorsal thalamic nucleus have been shown to impair memory performance of rats in the radial-arm maze (Stokes and Best 1988). We have recently found in a preliminary study that, unlike the hippocampus and amygdala, nicotinic antagonist infusion of DHβE into the mediodorsal thalamic nucleus causes significant improvements in working memory function (Levin et al. 2004a).

The anterior thalamic nuclei receive projections from the limbic system (Warburton et al. 2000), and lesions in these structures cause working memory impairments (Aggleton et al. 1991). The function of the nicotinic receptors in these thalamic nuclei has not yet been characterized, although muscarinic cholinergic receptors in this area have been shown to be important for memory as evidenced by the memory impairment seen after local infusions of scopolamine (Mitchell et al. 2002).

Midbrain dopaminergic nuclei

The midbrain dopaminergic nuclei, the ventral tegmental area (VTA) and substantia nigra, are the source of dopaminergic innervation of the forebrain. They have direct cholinergic innervation from the pedunculopontine nucleus and the dorsolateral tegmental nucleus (Gould et al. 1989), which innervate the nicotinic receptors located in these areas (Jones et al. 1999). Nicotinic receptors in the midbrain dopaminergic nuclei appear to be important for memory function. Local infusion of the nicotinic antagonist mecamylamine into the VTA or the substantia nigra causes significant working memory impairments (Levin et al. 1994). Interestingly, muscarinic cholinergic receptors in these areas seemed to be less critical for memory function inasmuch as local infusions of the muscarinic antagonist scopolamine into the VTA or into substantia nigra did not have effects on memory (Levin et al. 1994) when given at a dose range that did cause significant impairments when given to the ventral hippocampus (Kim and Levin 1996).

Other brain regions

Other brain regions are certainly sites for nicotinic mediation and modulation of cognitive function as well. GABAergic innervation of the mediodorsal thalamic nucleus from the ventral pallidum has been shown to play a crucial role for the involvement of the mediodorsal thalamic nucleus involvement in working memory function (Kalivas et al. 2001). The superior colliculus has dense nicotinic innervation and has been shown to be involved in attentional function by virtue of its involvement in controlling eye movements. The involvement of these areas and others remains to be defined with local infusion, lesion and complementary studies.

Clinical significance

The above-reviewed studies demonstrate the role of nicotinic receptor systems in cognition in laboratory animals and in nonnicotine-dependent adult humans. As nicotinic agonists have been shown to improve cognition in animal models of cognitive deficits, similar compounds might also benefit human patients with a wide range of cognitive disorders. The following section provides a review of the role of nicotinic receptors in the pathogenesis of a wide range of disorders and the effects of nicotine on cognition among patients with these conditions (Table 3).

Alzheimer's disease

Alzheimer's Disease (AD) is a debilitating disease characterized by loss of cognitive functioning, with onset typically after age 60. Early interest in relations between AD and nicotine arose from epidemiological data showing smokers to be at lower risk for the disease (Brenner et al. 1993; Wang et al. 1997). While more recent cohort studies call into question protection against AD by smoking (Almeida et al. 2002), several additional lines of evidence suggest that nicotinic receptors play an important role in the pathogenesis of the disorder. First, as with PD, postmortem assessment of the brains of patients with AD has revealed significant nicotinic receptor loss in cortex and striatum (Court et al. 2001, 2000a), although the degree of this loss appears to be less in former smokers than nonsmokers with the disease (Hellstrom-Lindahl et al. 2004). Furthermore, postmortem studies also show lesser plaque formation in former smokers with AD (Hellstrom-Lindahl et al. 2004). Consistent with these findings, a growing body of in vitro studies suggests that the accumulation of amyloid plaques, a central pathogenic factor in AD, is interfered with by nicotine (Ono et al. 2002; Utsuki et al. 2002). This promising line of investigation is beyond the scope of the current review. Finally, the most widely used currently available treatments are anticholinesterase inhibitors, which increase brain levels of choline and thus indirectly stimulate cholinergic receptors, providing additional evidence of the importance of neuronal cholinergic systems in the pathophysiology of AD.

Studies evaluating the effects of acute and chronic nicotine administration on cognitive function in AD patients tend to support enhancement of attention but not memory functions. In a double-blind, cross-over design in which patients wore nicotine or placebo patches for 4 weeks, White and Levin (1999) observed nicotine to reduce errors of commission and improve an index of attention in patients with AD. These findings were consistent with earlier work showing decreases in errors of intrusion following acute administration of nicotine intravenously (Newhouse et al. 1988) and improved accuracy and reaction times on the visual rapid information processing task (VRIP) following subcutaneous nicotine administration (Sahakian and Coull

Table 3 Effects of nicotine and nicotine agonists on learning, memory, and attention in different psychiatric populations

Compound	Diagnosis	Domain	Effects	Reference
Nicotine	Alzheimer's	Attention	+	White and Levin 1999
Nicotine	Alzheimer's	Attention	+	Newhouse et al. 1988
Nicotine	Alzheimer's	Attention	+	Sahakian and Coull 1994
Nicotine	Alzheimer's	Memory	0	Sahakian and Coull 1994
Nicotine	Alzheimer's	Memory	0	Snaedal et al. 1996
Nicotine	Alzheimer's	Memory	0	White and Levin 1999
Nicotine	Alzheimer's	Memory	0	Wilson et al. 1995
Nicotine	Alzheimer's	Learning	+	Wilson et al. 1995
ABT-418	Alzheimer's	Learning/Memory	+	Potter et al. 1999
Nicotine	Age-associated memory impairment	Attention	+	White and Levin 2004
Nicotine	Schizophrenia	Sensory gating	+	Adler et al. 1993
Nicotine	Relatives of individuals with schizophrenia	Sensory gating	+	Adler et al. 1992
Nicotine	Schizophrenia	Spatial information processing	+	Smith et al. 2002
Nicotine	Schizophrenia	Sustained attention	+	Depatie et al. 2002
Nicotine	Schizophrenia	Attention	+	Harris et al. 2004
Nicotine	Schizophrenia	Memory	0	Depatie et al. 2002
Nicotine	Schizophrenia	Memory	0	Harris et al. 2004
Nicotine	Schizophrenia	Memory	+	Myers et al. 2004
Nicotine	ADHD	Attention	+	Levin et al. 1996a-e
Nicotine	ADHD	Attention	+	Levin et al. 2001
Nicotine	ADHD	Inhibition	+	Potter and Newhouse 2004
ABT-418	ADHD	Attention	+	Wilens et al. 1999
Nicotine	Parkinson's	Attention	+	Kelton et al. 2000
Nicotine	Parkinson's	Various	0	Lemay et al. 2004
Nicotine	Down's syndrome	Attention	+	Bernert et al. 2001
Nicotine	Down's syndrome	Attention	+	Seidl et al. 2000
Nicotine	Tourette's syndrome	Attention	+	Howson et al. 2004

1994). Furthermore, these findings are consistent with data showing improvements in attention by chronic nicotine administration in individuals with age-associated memory impairment (White and Levin 2004).

In contrast to nicotine-induced improvements in attention, at least four studies have not found evidence of improvement of memory function by nicotine administration in AD patients (Sahakian and Coull 1994; Snaedal et al. 1996; White and Levin 1999; Wilson et al. 1995). However, despite these negative findings for memory function, transdermal nicotine has been shown to improve acquisition of information (Wilson et al. 1995) in AD patients, and the nicotinic agonist (ABT-418) has also been shown to improve components of both learning and memory in these patients (Potter et al. 1999).

Despite evidence of nicotine-induced improvements in cognitive function in AD, it is worth noting that, unlike other psychiatric populations, there is no evidence that individuals with AD are at a higher risk for smoking. While research on this issue is warranted, the reasons for unelevated risk might be due to the relatively late onset of symptoms when experimentation with cigarettes is infrequent. This may also result from the substantially lower numbers of nicotinic receptors that are present in the brains of people with AD (Court et al. 2000a, 2001), thus reducing the impact of nicotine in this population.

Schizophrenia

Smoking rates are disproportionately high for individuals with a lifetime history of schizophrenia (49.4%; Lasser et al. 2000) and even higher for individuals currently in treatment (79%; de Leon et al. 1995). These high rates of smoking among individuals with schizophrenia have typically been attributed to a number of factors including evidence of reversal of some of the cognitive deficits associated with the disease by nicotine (Adler et al. 1998) and possible self-medication of the side effects of neuroleptic medications (Levin et al. 1996e; McEvoy et al. 1995). Additional evidence of the involvement of nicotinic receptor system in the pathophysiology of schizophrenia comes from postmortem studies indicating a decrease in the number of $\alpha 7$ nicotinic receptors in the brains of patients with the disease (Court et al. 1999; Guan et al. 1999). Finally, large-scale cohort studies have shown smoking to be both predictive of schizophrenia (Weiser et al. 2004), but also potentially a protective factor (Zammit et al. 2003).

Sensory gating, or the dampening of the processing of subsequent stimuli until processing of a primary stimulus is complete, has long been known to be deficient in schizophrenia. Measured using the P50 auditory evoked potential procedure, individuals with schizophrenia and their first-degree relatives are more likely to exhibit the

same brain response to two closely presented auditory stimuli, while normal subjects typically exhibit a reduced or suppressed response to the second stimulus (Clementz et al. 1998). Smoking has been shown to improve sensory gating in overnight abstinent smokers with schizophrenia (Adler et al. 1993), and nicotine has been shown to transiently normalize sensory gating among nonsmoking relatives of individuals with schizophrenia who also exhibit the deficit (Adler et al. 1992). These improvements in auditory sensory gating may result from stimulation of α7 nicotinic receptors by nicotine, as evidence exists linking altered α7 nicotinic receptor number and functioning to schizophrenia (Court et al. 1999; Guan et al. 1999) and as animal studies have shown that the α7 nicotinic receptor mediates sensory gating (Luntz-Leybman et al. 1992).

Smoking and/or nicotine have also been shown in schizophrenia patients to improve cognitive functioning following overnight abstinence including spatial information processing (Smith et al. 2002) and sustained attention (Depatie et al. 2002). Further, nicotine gum (6 mg total) was shown to improve an index of attention in nonsmoking patients (Harris et al. 2004), suggesting that nicotine may result in an absolute increase in attentional performance in patients that cannot be wholly accounted for by alleviation of withdrawal. Despite positive findings for spatial processing and attention, several studies measuring memory functioning have found negative results (Depatie et al. 2002; Harris et al. 2004) However, one study (Myers et al. 2004) found improvement in delayed recognition following nasal nicotine spray administration, but only among smoking patients.

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder, which typically has its onset in childhood, is characterized by impairment of attention, problems with impulsivity, and an inability to inhibit behavior. The attentional impairments of ADHD with lesser hyperactivity have been found to persist into adulthood (Biederman 1998). Adults with ADHD are more likely to smoke (Pomerleau et al. 1995) and report starting smoking at an earlier age (Downey et al. 1996). Further, recent evidence from a large epidemiologic sample of young adults suggests that ADHD symptoms incrementally contribute to the risk of becoming a smoker (Kollins et al. 2005).

A large body of evidence has demonstrated that striatal dopaminergic transmission is dysregulated in ADHD (Castellanos and Tannock 2002), and psychostimulants, which cause an increase in striatal dopamine, are the most common treatments for the disorder. Likewise, the stimulation of dopamine release in the striatum by psychostimulants is thought to largely account for higher smoking rates in this population (Corrigall et al. 1994; Wonnacott et al. 1989). Consistent with this conceptualization, human neuroimaging studies have found evidence of greater dopamine precursor uptake in the basal ganglia in smokers compared to nonsmokers (Salokangas et al. 2000) and in the ventral striatum of smokers following smoking a single cigarette (Brody et al. 2004). In individuals with ADHD, similar effects of methylphenidate and nicotine on striatal dopamine transporter levels (Krause et al. 2002) have been observed.

Nicotine has been shown to improve indices of attention of adults with ADHD who were nonsmokers. In a laboratory study of the acute effects of nicotine, Levin et al. (1996b) observed acute nicotine (7 mg) to marginally reduce variability in reaction times across task conditions on the Conners' Continuous Performance Test (CPT). Consistent with these findings, in a follow-up study evaluating the effects of both acute (5 mg day^{-1}) and chronic nicotine (5–10 mg day^{-1} for 28 days) administration in ADHD nonsmokers, they found significant reductions in reaction time variability over the course of the CPT that were larger than those observed for methylphenidate alone or a combination of methylphenidate/nicotine (Levin et al. 2001).

In addition to attention-enhancing effects, there is preliminary evidence that nicotine may also attenuate difficulties with inhibition often observed in ADHD. In a small sample of adolescent nonsmokers with ADHD, Potter and Newhouse (2004) found a decrease in the time required to inhibit responding and improved performance on the Stroop task, a measure of the ability to inhibit reflexive responding, following acute (7 mg) nicotine administration.

The human studies reviewed above suggest that nicotine may improve cognitive performance and inhibition in individuals with ADHD, even when these individuals are nicotine-naïve and thus have not developed tolerance. These findings, along with others showing nicotine to improve mood and behavioral indices in individuals with ADHD (Levin 2001; Shytle et al. 2002), not only provide an explanation for higher rates of smoking among individuals with ADHD, but also suggest that nicotine and/or nicotinic compounds might be used to treat the disorder.

Parkinson's disease

Parkinson's Disease, considered primarily as a movement disorder, typically has its onset after age 55. Several lines of evidence suggest that nicotinic receptors play a role in the pathophysiology of PD. First, although still controversial, multiple retrospective and prospective studies suggest that tobacco smoking provides protection against the onset of PD (Allam et al. 2004; Gorell et al. 1999; Morens et al. 1995). Although specific mechanisms have not been fully elucidated, the prophylactic effects of smoking may be due to the chronic stimulation of dopaminergic systems by nicotine and possibly other smoke constituents and/or the neuroprotective actions of nicotine (for a review of putative mechanisms, see Quik and Jeyarasasingam 2000). Second, postmortem studies of PD patients' brains indicate a significant loss of nicotinic receptors compared to age-matched controls after controlling for tobacco use (Court et al. 2000b). Third, a number of published case

reports have suggested that PD symptoms might be relieved to some degree by nicotine administration (Fagerström et al.1994; Ishikawa and Miyatake 1993).

Several studies have evaluated the effects of nicotine on cognitive performance in patients with PD. In one study (Kelton et al. 2000), patients exhibited dose-dependent improvements following intravenous nicotine infusion on several measures of attention including reaction time; however, an age-matched control group was not included, making evaluation of these effects difficult. In another study, (Lemay et al. 2004), medicated PD patients were tested following wearing increasing doses of nicotine over a 25-day period (7 mg for 11 days, 14 mg for 11 days, and 21 mg for 3 days) and after a 2-week washout period. In patients who did not drop out of the study due to excessive side effects, no improvements on cognitive measures were observed. While this study did include an age-matched normal control group, subjects in that group did not receive nicotine and only underwent testing. Thus, while studies of the effects of nicotine on cognitive performance in PD patients have been conducted, additional placebo - and case-controlled studies evaluating cognitive performance following a range of nicotine doses are necessary before drawing any conclusions.

Other neurological and psychiatric conditions

Small-scale studies suggest that nicotine might provide some improvement in aspects of attentional functioning in individuals with Down's (Bernert et al. 2001; Seidl et al. 2000) and Tourette's syndromes (Howson et al. 2004). However, these studies have been small, and additional trials are needed.

Summary and conclusions

Nicotine has been shown to improve cognitive function among individuals with psychiatric conditions including schizophrenia, ADHD, PD, and AD. In each of these conditions, nicotinic receptors are thought to play a direct or indirect role in the pathophysiology of the condition as evidenced by postmortem analyses of brain tissue or human neuroimaging findings. Further, smoking rates are disproportionately high for individuals with schizophrenia and ADHD, and there is epidemiological evidence that smoking may have a neuroprotective effect in PD and AD.

Across the conditions reviewed in detail here, a number of studies have found evidence that nicotine can improve attention following both chronic and acute administration. This improvement may be due to a number of factors including nicotine stimulation of dopamine release in the striatum or direct stimulation of nicotinic neurons in the thalamus or other brain regions involved in attention (e.g., anterior cingulate cortex). Activation of nicotinic receptors in regions of the brain associated with arousal may also have the effect of enhancing attention.

There are some differences in the behavioral nature of the cognitive improvements caused by nicotine treatment in humans and experimental animals. As discussed above, in humans, the cognitive improvement induced by nicotine treatment is primarily seen with attention. In some cases, memory improvement has been seen, but this is a reversal of impairment caused by other treatments (e.g., haloperidol). In rats and monkeys, memory improvement is seen both with outright increased accuracy from intact baseline performance and reversal of performance impaired by drug treatments or lesions. While nicotine-induced attentional improvements have been seen in animal models, the memory-enhancing effects are more clearly demonstrated. Some of the differences between human and animal effects may lie in the nature of the testing. The cognitive function in animal models is for the most part on highly practiced tasks in mazes and operant procedures, whereas, in human studies, the test typically is given with little practice.

Identification of the critical receptor targets is often considered to be the primary mechanistic aid to the process of drug development. This idea is driven by the fact that drug candidates can be synthesized to more selectively activate one or another of the receptor subtypes. However, it is also important to determine the type of cognitive function affected by the differently acting nicotinic ligands.

The anatomic localization of the critical sites of action of nicotinic drugs for effects on cognitive function is important not only for better understanding of the basic organization of nicotinic involvement in cognitive function, but also for application to drug development. Although drugs are typically given systemically, neurotransmitters act in anatomically precise locations. Drugs by their nature are hormone-like in that they are distributed over wide areas of the body without anatomic direction according to intended function. When this distribution is imposed on a complex system in which actions on receptors in different areas have different meanings, the sum effect of a systemically delivered drug can be blurred by its actions on multiple systems. With the great anatomic diversity of nicotinic receptors in the brain, it is reasonable to presume that nicotinic receptors in different locations play different roles in neurobehavioral function. Nicotinic drug actions on some of these receptors may have positive effects on cognitive function, while the same actions on the same receptor subtypes in other brain areas may have negative actions, while still others may not be involved at all. For example, nicotine agonist effects in the mediodorsal thalamic nucleus appear to be opposite than the ventral hippocampus and the basolateral amygdala with regard to working memory function (Addy et al. 2003; Bettany and Levin 2001; Levin et al. 2002, 2004a). The same receptor action of a drug administered systemically would have mutually attenuating effects on memory function via simultaneous action in both areas.

Clinically, while nicotine has been shown to have beneficial effects on aspects of cognitive functioning, the only currently approved use of nicotine in the USA is as a smoking cessation aid. Nicotinic ligands that target specific receptor subtypes are in development and hold the promise

of being therapeutically useful treatments for a variety of cognitive dysfunctions. Determining the basic roles of nicotinic receptors throughout the brain for various aspects of cognitive function will greatly facilitate nicotinic therapeutic drug development.

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