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REVIEW

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Nicotinic acetylcholine involvement in cognitive function in animals

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Abstract Nicotinic cholinergic systems are involved with several important aspects of cognitive function including attention, learning and memory. Nicotinic cholinergic receptors are located in many regions of the brain, including areas important for cognitive function such as the hippocampus and frontal cortex. Nicotinic agonists have been found in rodent and non-human primate studies to improve performance on a variety of memory tasks. In a complementary fashion, nicotinic antagonists such as mecamylamine impair working memory function. In humans, similar effects have been seen. Nicotinic agonist treatment can improve attention, learning and memory and nicotinic antagonist treatment can cause deficits. To define the neural substrates of nicotinic involvement in cognitive function, three areas of investigation are underway. 1) Critical neuroanatomic loci for nicotinic effects are beginning to be determined. The hippocampus, frontal cortex and midbrain dopaminergic nuclei have been found to be important sites of action for nicotinic involvement in memory function. 2) Nicotinic receptor subtype involvement in cognitive function is being studied. There has been considerable recent work identifying nicotinic receptor subunit conformation including alpha and beta subunits. Nicotinic receptor subtypes appear to be associated with different functional systems; however, much remains to be done to determine the precise role each subtype plays in terms of cognitive function. 3) Nicotinic interactions with other transmitter systems are being assessed. Nicotine receptors interact in important ways with other systems to affect cognitive functioning, including muscarinic ACh, dopamine, norepinepherine, serotonin, glutamate, and other systems. Nicotinic function in clinical populations and potential for therapeutics has been investigated for Alzheimer's disease, Parkinson's disease, schizophrenia and attention deficit/hyperactivity disorder. Areas which need to receive greater attention are the exact anatomical location and the specific receptor subtypes critically involved in nicotine's effects. In addition, more work needs to be done to develop and determine the efficacy and safety of novel nicotinic ligands for use in the long-term treatment of human cognitive disorders.

Key words Nicotine · Memory · Cognition · Attention

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Introduction

This review is intended to provide an integrative update of progress in the understanding of nicotinic involvement with cognitive function. Considerable advancements have come in the last several years, including a better understanding of nicotinic receptor subtypes, the development of a variety of novel nicotinic ligands, better characterization of the cognitive effects of nicotinic drug treatment, determination of some of the critical neuroanatomic sites for nicotinic effects and better understanding to the interaction of nicotinic and other neural systems. This progress brings us much closer to understanding nicotinic involvement in cognitive function and the possible use of nicotinic agents for cognitive dysfunction.

Nicotinic receptor distribution

The autoradiographic localization of nicotinic receptors gives important insight concerning possible sites of action of nicotinic systems important for cognitive function. Studies by Kellar and Schwartz (Schwartz and Kellar 1983; Schwartz et al. 1984; Kellar et al. 1989), Collins and Marks (Marks et al. 1986, 1989) and Clarke et al. (Clarke et al. 1984; Clarke and Pert 1985; Clarke 1989) a decade ago gave detailed information about the anatomic localization of nicotinic receptors. They are distributed in a wide variety of brain areas. Nicotinic receptors in the hippocampus, cerebral cortex and nucleus

basalis magnocellularis (the nucleus basalis of Meynert in humans) may be particularly important for cognitive function. Initially, two major classes of nicotinic ACh receptors were identified using radioligand binding: subtypes binding (^{3}H)(–)-nicotine with high affinity, and those binding (^{125}I)α-bungarotoxin (BgT) (Arneric et al. 1995). This gave a good first approximation of the differential distribution of nicotinic receptor subtypes. However, more recently, the identification of different α and β subunits in the pentameric nicotinic receptor has given considerably more insight concerning nicotinic receptor subtypes. Some of the novel ligands recently developed have differential selectivity for these receptor subtypes.

Both α and β nicotinic receptor subunits have been found widely distributed in mammalian brain (Arneric et al. 1995). These subunits have been implicated as important in cognitive functioning. At least seven forms of the α subunit (α2, α3, α4, α5, α6, α7, α9) and 3 of the β subunit (β2, β3, β4) have been identified (Arneric et al. 1995; Wonnacott et al. 1996). In situ hybridization assays have localized the expression of subunits of nicotinic ACh receptors. The α4 subunit is highly expressed in several areas, including the ventral tegmental area and the substantia nigra pars compacta, major midbrain dopaminergic pathways. β2 subunits are found in almost all areas of the brain. Both the α4β2 subunit combination and α7 subunit have been especially implicated in learning and memory functions (below). The α4β2 subunits are found in areas that bind nicotine with high (>90%) affinity (e.g., the cortex, hippocampus, and interpeduncular nucleus (Sargent 1993; Arneric et al. 1995). The α7 subunits are distributed in areas with high-affinity binding sites for BgT (Caruncho et al. 1997). They are quite abundant in the Purkinje cell (del-Toro et al. 1997) and granule cell layers of the cerebellum (Caruncho et al. 1997) but are also present in diverse areas of the brain.

Nicotinic effects on cognitive performance

Behavioral pharmacology studies of nicotinic agonist and antagonist effects on cognitive performance have shown that nicotine and other nicotinic agonists can improve performance on cognitive tasks, while nicotinic antagonists such as mecamylamine can impair performance (see (Levin 1992, 1996; Decker et al. 1995; Brioni et al. 1997) for reviews). Although there are important exceptions to these general effects which help define the specificity of nicotinic involvement in cognitive function, the effects of nicotinic drug manipulations on performance accuracy have been seen with a variety of behavioral tests in rats, monkeys and humans.

Acute nicotine treatment

Acute treatment with nicotine or nicotinic agonists have been found to improve working memory function in the radial-arm maze (Levin 1994; Decker et al. 1995; Levin and Torry 1995; Levin et al. 1997a, 1998). The radial-arm maze consists of a central arena typically with eight arms extending outward. Additional arms can be added to provide a more challenging task and to provide more response locations to separately assess working and reference memory. In the most common radial-arm maze procedure, the subjects are reinforced for one entry per arm. For optimal performance, animals must adopt a "win-shift" strategy: once rewarded, responses must be switched and not repeated to receive additional reinforcement. Errors in this task are repeated arm entries; a greater number of arm entries before a repeat indicates better performance. The task directly measures spatial working memory, because animals need to remember locations recently visited in order to refrain from repeating entries. Working memory can be differentiated from reference memory in the radial-arm maze by consistently baiting certain arms and not others at the beginning of each session. We have used this technique to show the relative specificity of nicotine-induced improvement in working but not reference memory (Levin et al. 1996a, 1997a).

Acute nicotine has also been found to facilitate performance in passive avoidance (Brioni and Arneric 1993; Decker et al. 1994a; Zarrindast et al. 1996), Morris water maze (Socci et al. 1995) and delayed-match-to-sample (DMTS) tasks (Elrod et al. 1988; Jackson et al. 1989; Buccafusco et al. 1995, 1996). These tasks also directly measure working memory in that animals have to remember to inhibit an innate response (passive avoidance), remember the location of a platform in space (Morris water maze), or remember a target to decipher it from an array (DMTS).

Other selective nicotinic agonists have been found to facilitate performance in these tasks as well; findings from studies with these agents are summarized in Table 1. One of the promising benefits of selective agonists is that they can offer beneficial cognitive effects without the negative side effects such as cardiovascular changes, hypothermia and nausea that are often found with nicotine. For example, the predominately α4β2 agonist ABT-418 significantly enhanced delayed-match-to-sample performance in well-trained monkeys (Buccafusco et al. 1996). Although acute dosing did not have sustained effects, a finding in contrast to those of nicotine (Elrod and Buccafusco 1988; Levin et al. 1992; Terry et al. 1993), chronic administration of ABT-418 over 8 days did result in continued enhancement of performance with little signs of tolerance, suggesting that ABT-418 has potential as a well-tolerated, long-term treatment for cognitive deficits (Buccafusco et al. 1995). Studies with rodents have also found enhanced performance with ABT-418 in normal (Decker et al. 1994a; Terry and Decker 1997) and lesioned (Decker et al. 1994b) animals. Interestingly,

and in contrast to findings of studies with nicotine (Terry et al. 1996), mecamylamine (1.0 mg/kg) did not attenuate ABT-418-induced increases in performance of a delayed stimulus discrimination task in rats; these findings suggest that ABT-418 and nicotine are different in important ways, possibly with respect to activity at selective receptor subunits. It has been found that $\alpha 2\beta 4$ and $\alpha 4\beta 4$ are inhibited to a greater degree by mecamylamine than $\alpha 2\beta 2$, $\alpha 4\beta 2$, or $\alpha 7$ subunits (Chavez-Noriega et al. 1997), suggesting that differences in efficacy at these sites may account for differences in the behavioral effects of nicotine and ABT-418.

Several other nicotinic agonists also facilitate cognitive performance. For example, dimethylethanolamine (DMAE) (Levin et al. 1995), epibatidine (Levin 1996), and lobeline (Decker et al. 1993; Terry and Decker 1997) can increase working memory in rats on radial arm maze and delayed discrimination tasks. RJR-2403 is a newly developed nicotinic agonist that binds with greater selectivity than nicotine to rat cortical sites over peripheral muscle or ganglionic receptors (Bencherif 1996). Behaviorally, RJR-2403 reversed scopolamine-induced amnesia of a passive-avoidance response and also reversed impairments to both working and reference memory in the radial arm maze in rats with forebrain ibotenic acid lesions (Lippiello 1996).

The $\alpha 7$ agonist GTS-21 can also facilitate performance of a variety of tasks. For example, GTS-21 enhanced inhibitory avoidance responding in rats (Meyer et al. 1994). While this compound did not alter delayed-match-to-sample performance in monkeys on zero, short, or medium delay trials, it did significantly improve performance on long-delay trials. Administering GTS-21 10 min prior to testing increased performance from 52% to 61% correct, while treatment 24 h prior to testing increased performance from 52% to 64% correct, suggesting sustained effects of this compound (Briggs 1997). GTS-21 has also been found to enhance learning of a classically conditioned eyeblink response in older rabbits, suggesting that this compound might have beneficial effects in deficient organisms (Woodruff-Pak et al. 1994).

The specificity of the cognitive effects of nicotinic treatments can be discerned by the circumstances under which improvements are and are not seen. Improvement of working memory by nicotine is clearly seen, while reference memory is relatively unaffected by either acute (Levin et al. 1997a) or chronic nicotine administration (Levin et al. 1996a). Tasks that have a heavy component of proactive interference are also not improved by nicotine (Levin et al. 1997a) or can actually be impaired (Dunnett and Martel 1990). There is a proactive effect of nicotine enhancing the partial reinforcement extinction effect (Grigoryan and Gray 1996). Also, tasks that require animals to pay close attention (sustained attention or vigilance tasks) are only moderately (Evenden et al. 1993; Bushnell et al. 1998) or not at all facilitated by nicotine (Turchi et al. 1995) in animals, although this is typically not the case in humans (see below). However, failures to show enhanced performance following nicotine may be due to differences between studies regarding factors such as dose, strain, the nature of the task, and level of training (see Levin 1992 for a more complete review). For example, while it has been difficult to show facilitation in operant vigilance tasks with nicotine, nicotine can provide protection against the vigilance decrement induced by intracerebroventricular (ICV) administration of ethylcholine mustard aziridinium ion toxin in rodents (Miyata 1991).

Taken together, these results suggest that the nature of the task can profoundly influence nicotinic effects in animals. Performance on tasks with any component of proactive interference (PI) likely will not be enhanced by nicotinic agonists (Dunnett and Martel 1990), but may be facilitated by nicotinic antagonists (Levin 1996). PI is a phenomenon whereby information learned in the past interferes with the learning or memory of more recently presented material. For example, spatial alternation tasks have a high degree of PI because animals must remember previously executed responses and switch to make a different response. Certain "tracking" tasks (Evenden et al. 1993) also have a high component of PI because correct choices have a probability of occurring in a particular position according to the position of the last choice. In these tasks, then, animals get reinforced for remembering where the last response occurred, and then "forgetting" that information in order to make an alternative choice. What is probably happening with nicotinic agonists, is that memory is facilitated to such a degree that animals fail to "forget" their previous responses appropriately. Conversely, nicotinic antagonists such as mecamylamine can facilitate performance in these tasks by impairing memory of the last response choice (below).

Nicotine-induced memory improvements are blocked by the nicotinic antagonist mecamylamine (Andrews et al. 1994; Zarrindast et al. 1996; Levin et al. 1997a). Interestingly, the muscarinic antagonist scopolamine also reversed memory enhancement induced by nicotine (Terry et al. 1993). Nicotine does not appear to attenuate scopolamine-induced impairments, although comparable doses did reverse working memory deficits induced by mecamylamine (Levin et al. 1997a), and muscarinic agonists have been found to facilitate memory in a manner similar to nicotinic agonists (Brandeis et al. 1995). The effects of mecamylamine also appear be related to task difficulty and dose, since there are some studies that have not found mecamylamine-induced deficits (Clarke and Fibiger 1990), or have even found paradoxical improvements in performance (Levin et al. 1993b, 1994b; Moran 1993). As discussed above, these effects may be due to the degree of proactive interference involved in the task. Alternatively, mecamylamine has effects at NMDA receptors as well as nicotinic receptors. It is known that systemic treatment with NMDA antagonists such as dizocilpine (MK-801) disrupts memory performance (Levin and Bettegowda 1997); therefore, it is possible that mecamylamine-induced memory impairments are due to blockade of NMDA receptors. This possibility

Table 1 Effects of selective nicotinic agonists on cognitive function

Drug	Putative action	Dose/route	Species/gender	Task	Results	Reference
ABT –418	α4β2 agonist	0.062 μ mol/kg / ip	CD-1 mice / male	Passive avoidance	Increased retention	(Decker et al. 1994b)
ABT –418	α4β2 agonist	0.00126–0.126 mg/kg / ip	Wistar rats / male	Delayed stimulus discrimination	Improved performance	(Terry 1997)
ABT –418	α4β2 agonist	2–32.4 nmol/kg / im	Pigtail monkeys / 4 m, 2 f; rhesus monkeys / 2 male	Delayed match-to-sample	Increased performance, especially at longest delay intervals	(Buccafusco et al. 1995)
AF150(S)	Partial muscarinic M_1 agonist	1 mg/kg / po	Sprague-Dawley rats / male	Passive avoidance	Reversed AF64A-induced deficits	(Brandeis et al. 1995)
AF150(S)	Partial muscarinic M_1 agonist	0.5–5 mg/kg / po	Sprague-Dawley rats / male	Morris water maze	"Partially" improved performance	(Brandeis et al. 1995)
AF150(S)	Partial muscarinic M_1 agonist	0.5–5 mg/kg / po	Sprague-Dawley rats / male	Radial arm maze	Increased number of correct choices	(Brandeis et al. 1995)
Epibatidine	α3β2, α3β4 & α7 agonist	0.25–1 μ g/kg / sc	Sprague-Dawley rats / female	Radial arm maze	Increased performance early in training, but decreased late in training	(Levin et al. 1996e)
GTS-21	α4β2 agonist	32–130 nmol/kg / im	Pigtail monkeys / 3 male, 3 female	Delayed match-to-sample	Facilitated performance on long delay trials	(Briggs 1997)
GTS-21	α4β2 agonist	1 mg/kg / ip	Aged Sprague-Dawley rats / male	Active avoidance	Enhanced acquisition	(Arendash et al. 1995b)
GTS-21	α4β2 agonist	1 mg/kg / ip	Aged Sprague-Dawley rats / male	Lashley III maze	Enhanced acquisition	(Arendash et al. 1995b)
GTS-21	α4β2 agonist	1 mg/kg / ip	Aged Sprague-Dawley rats / male	17-arm radial maze	Improved learning and reference memory	(Arendash et al. 1995b)
GTS-21	α4β2 agonist	0.1–1 mg/kg / ?	Aged white rabbits / female	Eye-blink conditioning	Enhanced conditioning in aged rabbits	(Woodruff-Pak et al. 1994)
Lobeline	Mixed nicotinic agonist/antagonist	19 μ mol/kg / ip	Sprague-Dawley rats / male	Passive avoidance	Increased retention	(Decker et al. 1993)
Lobeline	Mixed nicotinic agonist/antagonist	1.0 μ mol/kg / ip	Sprague-Dawley rats / male	Water maze	Increased performance in septal lesioned rats	(Decker et al. 1993)
Lobeline	Mixed nicotinic agonist/antagonist	10 mg/kg / ip	Sprague-Dawley rats / male	Latent inhibition	Enhanced latent inhibition	(Rochford et al. 1996)
Lobeline	Mixed nicotinic agonist/antagonist		Sprague-Dawley rats / male	Stimulus discrimination	Improved accuracy for visual & auditory signals	(Terry et al. 1996)
RJR-2403	α4β2 agonist	0.3–1.2 μ mol/kg / sc	Sprague-Dawley rats / male	Radial arm maze	Reversed FBCS lesion-induced deficits, enhanced reference memory in normal rats	(Lippiello 1996)
RJR-2403	α4β2 agonist	0.6 μ mol /kg sc	Sprague-Dawley rats / male	Passive avoidance	Reversed scolopamine-induced deficits	(Lippiello 1996)

is unlikely, though, since deficits in working memory function have been caused with low doses of mecamylamine which do not have appreciable effects at NMDA receptors (Levin and Bettegowda 1997).

Chronic treatment

Interestingly, and in contrast to many of the other effects of nicotine, no tolerance is seen to the memory improving effects of chronic nicotine infusions. In fact, the memory improvement caused by nicotine seems to become more robust over time. We have found in a series of studies that chronic infusion of either a high dose of 12 mg/kg/day of nicotine (Levin and Rose 1990; Levin et al. 1990a, 1993a) or a more moderate dose of 5 mg/kg per day (Levin and Rose 1995; Levin and Torry 1996; Levin et al. 1993b, 1996a, c) of nicotine for 3–4 weeks significantly improves memory performance in the radial-arm maze. Improvement has been seen in both male and female rats. As shown in Fig. 1 there is an increase in entries to repeat (the number of correct entries until an error is made). Not only does chronic treatment enhance immediate performance, but these effects can persist well after nicotine withdrawal (Levin and Rose 1990; Levin et al. 1992, 1996a). Similar to findings with acute nicotine, chronic nicotine can enhance working memory performance in the 16-arm maze with no significant effect on reference memory (Levin et al. 1996a). Chronic treatment with agonists improves performance on other tasks as well, including one-way avoidance and the Lashley III maze (Arendash et al. 1995b). Chronic nicotine effects are less apparent in tasks susceptible to proactive interference such as T-maze alternation. We have found that the same dosing regimen (5 mg/kg per day for 4 weeks) which effectively improves memory performance in the radial-arm maze is not effective in the T-maze alternation task (Levin et al. 1997b).

Memory improvements found with chronic nicotine infusions can be blocked by concurrent chronic mecamylamine (Levin et al. 1993a). However, chronic nicotine can provide some protection against acute systemic mecamylamine challenges (Levin and Rose 1990). Nicotinic stimulation of nicotinic receptors blocked by mecamylamine may be essential for the induction but not for the expression of the chronic nicotine infusion induced memory improvement.

While nicotine can improve cognitive performance in fully functioning animals, nicotinic drugs also have profound effects in impaired organisms, or in normal organisms performing difficult tasks. For example, while nicotine increased DMTS performance in normal monkeys, enhancement was pronounced on the most difficult trials by almost a factor of 5 over all other trials (Jackson et al. 1989). Acute nicotine can also reverse deficits in DMTS performance caused by aging. Other studies have shown that acute nicotine facilitates performance in aged rats exhibiting deficits in spatial working memory (Cregan et al. 1989; Levin and Torry 1996), or in rats demonstrating poor passive avoidance performance due to a choline-deficient diet (Sasaki et al. 1991). Chronic nicotine does not appear to facilitate working memory performance in aged rats, possibly due to the decrease in functional nicotinic receptors in older organisms (Arendash et al. 1995a, b; Levin and Torry 1996). Acute nicotine treatment attenuates the memory deficit caused by septal lesion (Decker and Majchrzak 1991). Chronic infusions can reverse working memory deficits due to lesions of the fimbria and medial basalocortical projection (Levin et al. 1993b). Although it appears that chronic nicotine has no direct effects on working memory in aged animals, acute nicotine injection is effective in reversing aging-induced memory impairment (Levin et al. 1996a).

Critical anatomic loci for nicotinic effects

Bringing together the behavioral pharmacology and neuroanatomic approaches, recent studies have used lesion and local infusion studies to help define which areas of the brain are important for nicotinic involvement in cognitive function. Subsequently greater detail can be garnered with this approach to determine specifically which aspects of cognitive functions (attention, memory, learning, etc.) involved which different anatomic nicotinic systems.

The hippocampus has long been known to be a structure critically important for attention and memory (for review, see Jarrard 1995). Studies have found that hippocampal ACh increases significantly in rats that have learned a task when compared to matched controls (Fadda et al. 1996). Nicotine facilitates hippocampal synaptic activity (Gray et al. 1996) and increases hippocampal LTP (Hamid et al. 1997). Chronic nicotine-induced increases in nicotinic binding in the dorsal hippocampus and entorhinal cortex are positively correlated with nicotine induced facilitation of learning rate but not with asymptotic performance levels (Abdulla et al. 1996). Local infusions of nicotinic antagonists mecamylamine were found by Ohno and co-workers to impair memory performance (Ohno et al. 1993). We found a very similar effect with radial-arm maze choice accuracy impaired after infusion of mecamylamine, an $\alpha 3\beta 4$ antagonist, into the ventral hippocampus (Kim and Levin 1996). More recently, as shown in Fig. 2, we have found that infusion of the $\alpha 4\beta 2$ antagonist DHβE or the $\alpha 7$ antagonist MLA into the ventral hippocampus also impair working memory performance in the radial-arm maze (Felix and Levin 1997).

Lesion models have also provided insight into nicotinic hippocampal involvement in cognitive function. Nicotine reverses attentional and memory impairments caused by basal forebrain lesions in rats (Grigoryan et al. 1994a, b, 1996; Muir et al. 1995) or marmosets (Ridley et al. 1986). Ablation of the septum, the source of the septohippocampal pathway, or knife-cut lesions of the fimbria-fornix, the pathway from the septum to the hippocampus, each cause significant deficits in memory performance but do not prevent the expression of nico-

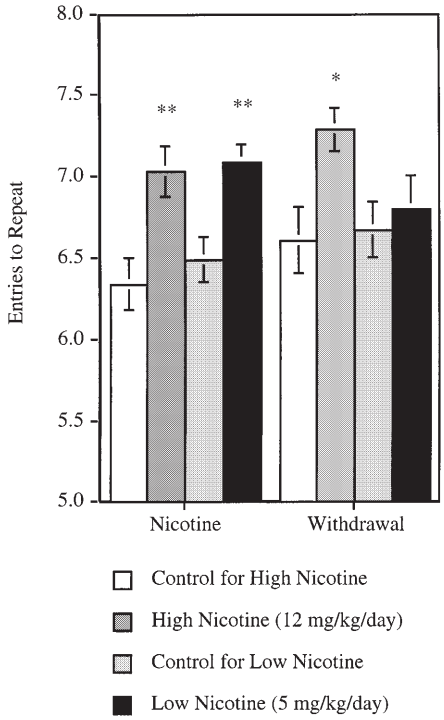

Fig. 1 Chronic nicotine effects on radial-arm maze choice accuracy (entries to repeat mean±SEM). **P*<0.05, ***P*<0.005

tine-induced improvements in memory performance. Studies from the laboratory of Decker (Decker and Majchrzak 1991; Decker et al. 1992) as well as our own (Levin et al. 1993b) have shown that the full extent of nicotine-induced memory improvement is seen after these lesions; nicotine effectively reverses the lesion-induced deficits. Nicotine also reinstates the sensory gating response lost with fimbria-fornix transactions (Bickford and Wear 1995). Thus, the nicotinic receptors on the terminal endings of the septohippocampal neurons are not necessary for the expression of the nicotine-induced memory improvement. Nicotinic receptors on cell bodies within the ventral hippocampus seem to be important for memory function. Local infusions of the nicotinic antagonist mecamylamine into the ventral hippocampus impairs working memory function (Kim and Levin 1996). As shown in Fig. 2, we have found that local ventral hippocampal infusions of nicotinic receptor subtype specific antagonists have shown that both DHβE, an α4β2 nicotinic antagonist, and MLA, an α7 nicotinic antagonist, also cause significant impairments in radial-arm maze working memory performance (Felix and Levin 1997). In more recent work in our laboratory, we have found that lesions of the cell bodies in the hippocampus do have dramatic effects on nicotine and nicotinic antagonist effects on working memory function. Ibotenic acid lesions of the ventral hippocampus do not impair memory performance by themselves, but they do eliminate chronic nicotine-induced memory improvements (Levin, unpublished data, 1998). In a similar fashion, ibotenic acid lesions made during infancy eliminate the amnestic effects of mecamylamine (Chambers et al. 1996).

The frontal cortex and forebrain areas are also important for memory function. In particular, lesions of the medial frontal cortex (Broersen 1995) as well as of the forebrain cholinergic pathway (Hodges et al. 1991, 1992; Turner et al. 1992) have been found significantly to impair memory performance. Importantly, disruptions of the forebrain cholinergic projection system appear to affect attentional processes rather than memory. Evidence for this comes from studies demonstrating that although forebrain lesions caused disruptions of working and reference memory on the radial arm maze, cholinergic-rich fetal grafts into this area improved performance, but not when extra-maze cues were obscured (Hodges et al. 1991). Nicotinic receptors in the frontal cortex have been found to be important for memory performance (Granon et al. 1995; Vidal and Changeux 1996). The nicotine antagonist bungarotoxin injected into the prefrontal cortex significantly decreased delayed-match-to-sample performance in rats (Granon et al. 1995), while nicotine overcame performance decrements on the radial-arm maze induced by both ibotenate and quisqualate lesions (Turner et al. 1992). Loss of nicotinic receptors in the frontal cortex may be clinically important for the cognitive impairment of Alzheimer's disease (Nordberg 1994; Nordberg and Winblad 1986).

The midbrain dopamine nuclei, the ventral tegmental area (VTA) and substantia nigra (SN) have high ratios of nicotinic receptor binding. Local infusions of mecamylamine into these areas causes significant deficits in radial-arm maze working memory performance (Levin et al. 1994a). We have shown that nicotinic receptors in the midbrain dopaminergic nuclei, the ventral tegmental area (VTA) and substantia nigra (SN), are important for memory. Local infusions of the nicotinic antagonist mecamylamine into the VTA and SN caused significant deficits in working memory deficits in the radial-arm maze. In contrast, nicotinic receptors in the nucleus accumbens appear to be less important for memory. Mecamylamine infusion into the nucleus accumbens at the same doses had no discernible effect on memory performance (Kim and Levin 1996).

Critical receptor subtypes for nicotinic effects

Considerable progress has been made concerning the identity and structure of nicotinic receptor subtypes. Nicotinic acetylcholine receptors contain at least one type of α-subunit and one type of β-subunit (Sargent 1993). The beta-2 subunit appears to be the most widely expressed in the central nervous system (Wada et al. 1989), although other prominent subunit combinations including the α4β2, α3β2, and α7 exist as well. Now, the functional roles played by these subtypes are being discovered.

Hippocampal α4β2, α3β2, and α7 receptors appear to be important for working memory functions. Studies have

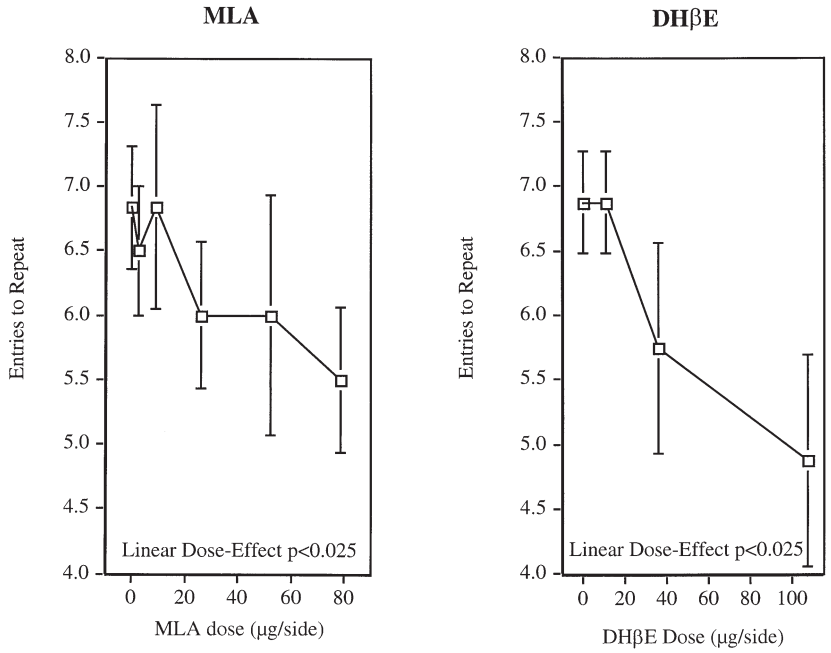

Fig. 2 MLA and DHβE effects when infused into the ventral hippocampus (entries to repeat mean±SEM)

shown that most hippocampal neurons had nicotinic receptors that responded to nicotine with a type IA nicotinic current characterized by rapid desensitization and blockade by MLA (Alkondon and Albuquerque 1993; Castro and Albuquerque 1993), characteristic also of α7 nicotinic receptors (Schoepfer et al. 1990; Séguéla et al. 1993). Fewer neurons had receptors that responded with type II currents and were blocked by DHβE and type III currents which were blocked by mecamylamine and were more slowly desensitized (Alkondon and Albuquerque 1993). Some neurons showed a mixed response, termed type IB, which was partially blocked by either MLA or DHβE but were completely blocked by both antagonists (Alkondon and Albuquerque 1993). The pharmacological and kinetic properties of these currents support their correspondence to α7 (type 1A), α4β2 (type II), and α3β4 (type III) nicotinic receptor subtypes (Albuquerque et al. 1997). However, it is important to note that one hippocampal neuron can express more than one nicotinic receptor subtype (Alkondon and Albuquerque 1993). ACh evoked electrical response in hippocampal neurons in an in vitro preparation were blocked by MLA (Barbosa et al. 1996). ACh and anatoxin elicited currents were blocked in hippocampal neurons by either MLA or DHβE (Alkonodon and Albuquerque 1990). NMDA and α7 receptors are located on similar areas of hippocampal neurons. As described above and shown in Fig. 2, we have found that local infusions of either MLA or DHβE into the ventral hippocampus significantly impairs working memory performance on the radial-arm maze (Felix and Levin 1997).

The α7 type of nicotinic receptor appears important in cognitive functioning It is found in high concentrations in the rat hippocampus (Segal et al. 1978; Clarke et al. 1984; Clarke and Pert 1985; Pauly et al. 1989; Freedman et al. 1993). Transcripts of α7 receptors are found throughout the main parts of the limbic system (Séguéla et al. 1993). α7 receptors are found on hippocampal interneurons and seem to regulate neurite outgrowth and survival. Little is currently known about the functional role of α7 type nicotinic receptors in the brain. They may be important for hippocampal processing of information. Central blockade of α7 nicotinic receptors with α-bungarotoxin or (+)-tubocurarine disrupted habituation of evoked responses in the hippocampus to repeated auditory stimuli, while blockade of α4β2 nicotinic receptors or muscarinic receptors was ineffective (Luntz-Leybman et al. 1992). Both α4β2 and α7 nicotinic receptors in the hippocampus may be important for aspects of cognitive function.

β2 units are also important in cognitive functioning. For example, it has been demonstrated that mice homozygous for a β2-subunit mutation (β2-/β2-) do not demonstrate high-affinity binding sites for nicotine; behaviorally, these mice fail to show facilitation of a passive avoidance task following nicotine while normal controls do, suggesting that β2 sites are important for nicotinic memory enhancement (Picciotto et al. 1995). We have found that nicotinic antagonists with differential blockade of α3β2 (mecamylamine), α4β2 (DHβE) and α7 (MLA) nicotinic receptors impair working memory. Local infusion of the nicotinic antagonist mecamylamine, DHβE, and MLA into the hippocampus impairs working memory in rats (Ohno et al. 1993; Kim and Levin 1996).

Nicotinic interactions with other transmitter receptor systems

The brain is an organ of connections. Thus no receptor system acts in isolation from others in providing the functional output of the brain. Nicotinic receptors are no exception. In fact, they provide a good case in point, demonstrating the interactions among transmitter sys-

tems in the neural basis of cognitive function. Nicotine induces the release of a variety of neurotransmitters including acetylcholine, dopamine, norepinepherine, serotonin and glutamate. Other interactions between nicotinic receptors arise for the neural circuitry involved in cognitive function.

Muscarinic acetylcholine

Because nicotine stimulates acetylcholine release nicotine can have effects mediated secondarily via muscarinic ACh receptors. We have found that nicotine-induced improvement in working memory performance is reversed by the muscarinic antagonist scopolamine (Levin and Rose 1991). The nicotinic antagonist mecamylamine has mutually potentiating effects with the muscarinic antagonist scopolamine (Levin et al. 1989).

Dopamine

Nicotinic receptors are heavily concentrated on midbrain dopaminergic nuclei (see above). Nicotine administration promotes dopamine efflux in the striatum and nucleus accumbens (Lichtensteiger et al. 1982), and also increases extracellular concentrations of dopamine in the cortex (Summers and Giacobini 1995). Conversely, blockade of D_1 receptors can inhibit ACh release, while their stimulation enhances ACh transmission. Both stimulation and blockade of D_2 receptors reduces ACh release (DiChiara et al. 1994). Nicotine-induced dopamine release has been posited to be important for nicotine dependence. The importance of nicotinic-dopaminergic interactions for cognitive function has also been documented. For example, we have shown that DA drugs can reverse working memory deficits caused by knife cut lesions to the medial cholinergic basalocortical pathway (McGurk et al. 1992). Acute nicotinic agonist and antagonist effects on memory performance have significant interactions with both D_1 and D_2 systems (McGurk et al. 1989a, b; Levin et al. 1990b; Levin and Rose 1992, 1995; Levin and Eisner 1994). Infusion of the nicotinic antagonist mecamylamine into the midbrain dopaminergic nuclei significantly impairs working memory performance in the radial-arm maze (Levin et al. 1994a). Other studies have shown that nicotine disrupts latent inhibition learning, an effect that can be blocked by pretreatment with the DA antagonist haloperidol (Joseph et al. 1993). Studies in our laboratory have also shown that the memory-enhancing effects of both acute (Levin and Rose 1995; Kim and Levin 1996) and chronic nicotine (Levin et al. 1996c) interact with DA systems (see Levin and Rose 1995, for a more complete review). For example, chronic (5 mg/kg per day) nicotine increased the memory impairment caused by the D_1 agonist dihydrexidine and decreased the improvement caused by the D_1 antagonist SCH 23390 (Levin et al. 1996a). These findings suggest that nicotinic functions are important in cognitive disorders traditionally believed to involve primarily DA mechanisms, including attention deficit/hyperactivity disorder and schizophrenia. Interestingly, we have recently shown that there is a significant relationship between the extent of DA binding and working memory function, while the relationship between nicotinic binding and memory is weak (Levin et al. 1997c).

Serotonin

Riekkinen and co-workers have investigated the interactions of nicotinic and serotonergic systems. A variety of studies involving anatomic or pharmacologic lesions of serotonin (5-HT) neurons have shown effects suggesting interactions with ACh functioning (Riekkinen et al. 1991). Other work has shown that the selective 5-HT_3 antagonist ondansetron stimulates release of cortical ACh and can enhance cognitive performance in rodents (Carey et al. 1992) and primates (Barnes 1990). In addition, depletion of serotonergic neurons by PCPA administration has not been found to affect working memory or passive avoidance performance alone, but it can significantly alter the effects of both nicotine and mecamylamine. PCPA lesions aggravated the working memory deficit caused by mecamylamine and decreased the extent of nicotine-induced improvements in a water maze spatial reference task (Riekkinen et al. 1993). However, this compound did not exacerbate the effects of scopolamine on cognitive functioning in elderly humans (Little et al. 1995), nor did it alter the accuracy deficit caused by AMPA-induced lesions of the nucleus basalis magnocellularis in rats (Muir et al. 1995). However, the 5-HT mixed agonist/antagonist *m*-CPP significantly exaggerated the effects of scopolamine on several cognitive, behavioral, and physiological measures in elderly humans (Little et al. 1995), providing additional evidence that 5-HT systems interact in important ways with ACh to affect cognition.

Norepinephrine

Centrally administered (ICV) nicotine increases norepinephrine in the substantia nigra, cingulate cortex, and pontine nucleus (Toth et al. 1992). Moderately high to high doses (0.4–1.2 mg/kg) of peripherally injected (SC) nicotine release norepinepherine in the cortex (Summers and Giacobini 1995), hippocampus (Brazell et al. 1991), and the dorsal noradrenergic bundle (Mitchell et al. 1990). Increases in hippocampal NE appear to be mediated by actions at the cell bodies of noradrenergic neurons, which are located in the locus coeruleus (Mitchell 1993). Not only does nicotine itself increase NE concentrations, but the nicotinic agonists epibatidine and lobeline increase NE in the hippocampus as well (Sershen et al. 1997). However, studies by Gray and co-workers have found limited interaction between nicotine and NE on memory tasks, although nicotine ap-

parently interacts with NE to increase resistance to extinction (Gray et al. 1994). For example, while nicotine facilitated performance in rats with lesions of the forebrain cholinergic projection system (Grigoryan et al. 1994a, b), treatment with the noradrenergic antagonist propranolol did not block these effects (Grigoryan et al. 1994b). These results suggest that nicotine-induced reversal of the lesion effects is due to mechanisms other than NE activation.

Glutamate/NMDA

Neurophysiologic studies have shown that glutamate release is also stimulated by nicotine treatment (Toth et al. 1992; McGehee et al. 1995). Co-administration of kynurenic acid, a glutamate antagonist, blocked nicotine-induced increases in extracellular glutamic acid (Toth et al. 1992). Interestingly, this antagonist also blocked dopamine increases associated with nicotine administration, suggesting that nicotine effects on dopamine release are mediated by glutaminergic mechanisms. In behavioral studies, we have found that nicotine attenuates the amnestic effects of dizocilpine (MK-801). Dizocilpine (0.1 mg/kg) causes substantial deficits in both working and reference memory on the 16-arm radial maze (Levin and Bettegowda 1997). In addition, this dose of dizocilpine eliminated the memory improvement caused by 0.2 mg/kg nicotine. However, a higher dose of 0.4 mg/kg nicotine, which usually is too high to cause a significant improvement in working memory performance, did cause a significant reduction in dizocilpine-induced deficits in both working and reference memory. It is currently not known why nicotine does not have effects on reference memory but is effective in reversing dizocilpine effects on reference memory.

Other neurotransmitter and hormonal systems

Other transmitter systems such as GABA, opioid, and histaminergic also may be involved in nicotinic effects on cognitive function. Nicotine can cause at least a transient increase in GABA release in both the substantia nigra and globus pallidus (Kayadjanian et al. 1994). Effects in the substantia nigra are blocked completely by pretreatment with the dopamine D_1 antagonist SCH 23390, while DA antagonists have only moderate effects on GABA release in the globus pallidus, suggesting that nicotine can differentially modulate GABA transmission in these areas (Kayadjanian et al. 1994). Extracellular levels of several amino acids, including glycine and taurine, are also increased following central administration of nicotine (Toth et al. 1992). Additionally, nicotine significantly reduces brain levels of substance P (Naftchi et al. 1988). It has been shown that memory improvements found with the neuropeptide lysine vasopressin can be blocked by pre-treatment with the centrally acting antagonist mecamylamine but not the peripherally-acting blocker hexamethonium (Faiman et al. 1988). These results suggest an important relationship between nicotinic and neuropeptide effects in the brain (Sershen et al. 1995). Nicotine also potently stimulates cortisol release (Pauly et al. 1992). Interestingly, it appears that corticosterone acts as a nicotinic antagonist, as adrenalectomy causes increases in, and stress causes decreases in reactivity to nicotine (Pauly et al. 1992). The relationship of cortisol release to the cognitive effects of nicotine is currently unclear.

Nicotinic function in clinical populations and potential for therapeutics

Nicotine and nicotinic ligands have the promise for novel treatments for a variety of cognitive disorders including those associated with Alzheimer's disease, Parkinson's disease, schizophrenia and attention deficit/hyperactivity. Alternate forms of delivery such as the nicotine skin patch reduce some of the health risks and abuse liability. Development of more specific nicotinic sister drugs may separate the cognitive enhancing effects of nicotine from its cardiovascular, developmental and reinforcing effects so that adverse side effects can be further reduced.

Alzheimer's disease has received the most attention to date as a therapeutic target for nicotinic drugs (Nordberg 1994). Nicotinic receptor binding has been found to be substantially reduced in the cortex and hippocampus of Alzheimer's patients (Nordberg and Winblad 1986; Kellar et al. 1987; Perry et al. 1987; Kellar and Wonnacott 1990; Nordberg et al. 1992). Smoking has been found by several studies to reduce the incidence of Alzheimer's disease (Brenner et al. 1993; Ishikawa 1993; Lee 1994; Van Duijn et al. 1994, 1995); see also Newhouse et al. 1997 for a more complete review. This is especially clearly seen in subpopulations with a genetically associated high risk for Alzheimer's disease (Van Duijn et al. 1994, 1995). Nicotine injections have been found to improve attention and memory (Newhouse et al. 1988; Sahakian et al. 1989; Jones et al. 1992). More recently, longer 8-day nicotine patch administration has been found to improve learning rates in Alzheimer's patients (Wilson et al. 1995). Recently, we have found that longer, 4-week nicotine skin patch administration also significantly improves attentional processing in Alzheimer's disease patients. This highlights one of the major advantages of nicotinic therapy for cognitive impairments, there does not appear to be tolerance to the therapeutic effect.

Parkinson's disease has been found in some preliminary studies to be attenuated by nicotine administrations (Newhouse et al. 1997). There is a cognitive deficit associated with Parkinson's disease. This is related to the loss of dopaminergic projections to the substantia nigra, an area shown to interact with cholinergic functioning (above). In addition, a similar loss of cholinergic cells in the basal forebrain nuclei, as occurs in Alzheimer's disease, has been described in Parkinson's disease (White-

house et al. 1983). Consistent with this work, patients with Parkinson's disease and dementia have been found to have a loss of cholinergic markers in the cortex (Perry and Dick 1985). Several studies show that smokers have a lower than expected incidence of Parkinson's disease, suggesting that nicotine provides a protective effect (Baumann 1980; Baron 1986; Morens 1995). Although epidemiological studies do not confirm that nicotine is a protective agent, nicotine can counteract the effects of MPTP-induced lesions in mice, an animal model for Parkinson's disease (Sershen and Lajtha 1987). Another study showed that smoking a cigarette reduced tremor, rigidity, bradykinesia, and gait disturbances in patients with early-onset Parkinson's disease, an effect that lasted from 10 to 30 min (Ishikawa 1993). Taken together, these results suggest that nicotine treatment may provide beneficial effects in Parkinson's disease.

Schizophrenics smoke at rates substantially higher than the general population. They smoke at rates of about 80% (Hughes et al. 1986). They may smoke as a form of self-medication to attenuate the adverse effects of dopamine receptor blockers such as haloperidol which are commonly used antipsychotics. McEvoy and co-workers found that schizophrenic patients with higher doses of haloperidol smoke more (McEvoy et al. 1995). In a recent study of schizophrenic patients (Levin et al. 1996b), we have found that nicotine given via a skin patch significantly reduces haloperidol-induced deficits in delayed matching to sample and complex reaction time. In addition to nicotine-induced attenuation of the deficits caused by dopamine receptor antagonist treatment, nicotine may also have effects in the attenuation cognitive deficits primarily associated with the primary cognitive deficits associated with schizophrenia. Freedman and co-workers have found that smoking attenuates the sensory gating deficit seen in schizophrenics and their family members (Alder et al. 1992, 1993). They have also found that schizophrenics have lower numbers of nicotinic receptors in the hippocampus (Freedman et al. 1995). We also found that regardless of haloperidol dose, nicotine caused an improvement in performance consistency on a continuous performance attention task (Levin et al. 1996b).

Attention deficit/hyperactivity disorder (ADHD) is attenuated by nicotine administration, which may explain the reason why people with ADHD smoke at rates about double the rest of the population (Barkley et al. 1990; Pomerleau et al. 1996). We have found that nicotine administration via skin patches significantly decreases symptoms in adults with ADHD (Conners et al. 1996; Levin et al. 1996d). Importantly, we have found that this effect is evident even in non-smoking adults with ADHD. Thus, the nicotine effects seen are not due simply to alleviating nicotine withdrawal symptoms. Most recently, we have found that nicotine administration improves attentiveness in nonsmoking adults without ADHD (Levin et al. 1998). Nicotine stimulates the release of dopamine, a mechanism of action it has in common with the currently used therapeutic drugs for ADHD: amphetamine and methylphenidate.

Summary and conclusions

Nicotinic systems are clearly important for cognitive function, in particular attentional and memory performance. The behavioral nature of the effect has help define the specificity of the effect. Working memory is improved, but reference memory is relatively unaffected. Tasks that have a heavy component of proactive interference are not improved by nicotine or can actually be impaired. While several studies have failed to find significant facilitation of vigilance task performance with nicotine, these failures may be the consequence of the nature of the task, baseline rates of behavior, and/or dose. Nicotinic-induced improvements in a variety of cognitive functions including learning, attention and memory have been documented in several different species including rats, monkeys, and humans performing a range of tasks.

Promising areas for nicotine research in the future are the determination of the role of the different nicotinic receptor subtypes in the neural substrates of cognitive function, the particular parts of the brain in which nicotinic receptors are important, the non-nicotinic systems which interact with nicotinic systems with regard to cognitive function, and the utility of nicotinic ligands for treatment of cognitive disorders. One important area for investigation is the relationship of nicotinic involvement in cognitive function to nicotinic involvement in other types of function. For example, is there a relationship of nicotinic effects on reinforcement to its effects on cognitive function. Is nicotine's effect on arousal related to its effect on cognitive function?

Nicotinic systems are now well documented to be important components in the neural substrates of cognitive function. These effects may provide avenues for the development of novel therapeutic treatments for a variety of cognitive dysfunctions such as are seen in Alzheimer's disease, attention deficits/hyperactivity disorder, schizophrenia and Parkinson's disease. As the elegant work in the molecular biology of nicotinic receptor subtypes helps in the development of receptor subtype selective ligands, further breakthroughs concerning nicotinic involvement in cognitive function will be made.

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