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Effects of nicotinic stimulation on cognitive performance

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Recent advances in studies of nicotinic agents in humans have begun to more carefully define cognitive operations that can be influenced by nicotinic stimulation and/or blockade. Careful separation of the cognitive domains affected by nicotinic stimulation has identified attentional performance as the most likely candidate to be positively influenced by nicotinic receptor activation. Studies of the effects of nicotinic systems and/or nicotinic receptor stimulation in pathological disease states such as Alzheimer's disease, Parkinson's disease, attention deficit/hyperactivity disorder and schizophrenia show the potential for therapeutic utility of nicotinic drugs. In contrast to studies in pathological states, studies of nicotine in normal-non-smokers tend to show deleterious effects. This contradiction can be resolved by consideration of cognitive and biological baseline dependency differences between study populations in terms of the relationship of optimal cognitive performance to nicotinic receptor activity. Although normal individuals are unlikely to show cognitive benefits after nicotinic stimulation except under extreme task conditions, individuals with a variety of disease states can benefit from nicotinic drugs. Attentional function/dysfunction may serve as an endophenotypic therapeutic target for nicotinic drug development.

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Current Opinion in Pharmacology 2004, **4**:36–46

This review comes from a themed issue on Neurosciences
Edited by Joseph Coyle

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2003.11.001

Abbreviations

AD	Alzheimer's disease
ADHD	attention deficit/hyperactivity disorder
CNS	central nervous system
fMRI	functional magnetic resonance imaging
MCI	mild cognitive impairment
nAChR	nicotinic receptor
PD	Parkinson's disease
PET	positron emission tomography
VSWM	visuospatial working memory

Introduction

Neuronal nicotinic receptors (nAChRs) are found throughout the central nervous system (CNS). These receptors are composed of two types of subunits, α and β, of which nine α (α2–α10) and three β (β2–β4) have been found in vertebrates [1–3]. Nicotinic innervation of the hippocampus, amygdala and frontal cortex has been demonstrated to be vital to memory function [4•].

Nicotine is one of over 4 000 compounds found in tobacco smoke, among which is found a variety of carcinogens as well as other toxic compounds such as carbon monoxide, heavy metals and cyanide. However, nicotine administered independent of tobacco appears to be relatively safe [5]. There is a large amount of literature showing that nicotine skin patches are safe and have very low abuse liability [6,7].

The behavioral effects of nicotine are complex and belie a simple classification of nicotine as either a stimulant or depressant. Determinants of the effect of nicotine on human behavior include pharmacological variables (e.g. dose, route of administration) and subject differences (e.g. gender, personality variables). Whether, and how, subjects control the administration of nicotine appears to have significant impact on its cognitive effects. Such effects need to be taken into consideration when considering the use of novel nicotinic agonists for possible beneficial behavioral effects.

This review focuses on recent advances in studies of the cognitive effects of nicotine in smokers and normal volunteer populations, and contrasts those studies with trials of nicotinic stimulation in pathological disease states. These disease states represent the most likely targets for nicotinic drug development and include Alzheimer's disease (AD), mild cognitive impairment (MCI), Parkinson's disease (PD), schizophrenia and attention-deficit/hyperactivity disorder (ADHD). In an attempt to resolve the conflicting results of generally negative studies in normal volunteer populations and positive studies in pathological disease states, we focus on an analysis of cognitive and neurobiological baseline differences between study populations. Finally, the concept of attentional function and dysfunction as an endophenotype for nicotinic drug development is introduced, and we offer the hypothesis that this target is orthogonal to disease diagnosis and offers the best target for the therapeutic effects of nicotinic agents.

Nicotinic receptor stimulation as a cognition-enhancing strategy in 'normals'

Studies in humans have spanned several decades and consist mostly of experiments utilizing cigarettes to administer nicotine, usually to smokers deprived of cigarettes for some period of time. Although nicotine might

'improve' performance in deprived smokers, it appears that this improvement is usually limited to restoring pre-deprivation performance, which clearly declines during cigarette withdrawal [8]. Enhancement of normal non-deprived smokers and nonsmokers with nicotine has been more difficult to demonstrate. In studies with humans, nicotine has been shown to improve performance in smokers on attentionally and cognitively demanding vigilance tasks [9–11]. Recent work has shown that attentional improvements are seen even in the absence of nicotine withdrawal effects [12].

Recent studies of the effects of nicotine and/or smoking on cognitive performance in smokers have attempted to mitigate or minimize many of the problems associated with cognitive studies utilizing drug-dependent individuals. Bell, Taylor, Singleton, Henningfield and Heishman [13] confirmed that smoking deprivation impairs cognitive performance and that re-administering cigarettes briskly relieves this performance decrement. Utilizing electrophysiological assessment, nicotine administration to smoking-deprived smokers improved power indices of electroencephalogram arousal, with shortened reaction times increasing P300 (evoked potential occurring 300 msec after stimulus presentation) amplitudes [14]. Under conditions of suboptimal alertness, smokers who were administered nicotine showed improved and constant performance during a sustained choice reaction time task, suggesting that nicotine has an enabling effect on sustained cognitive effort, at least in this population [15]. Utilizing the strategy of administering a transdermal nicotine patch to smokers participating in a smoking withdrawal study, Cook, Gerkovich, Graham, Hoffman and Peterson [16] did not find that nicotine administration mitigated the cognitive effects of smoking cessation and hypothesized that performance decrements noticed by smokers during cessation may be related to affective disturbances rather than cognitive impairment. Utilizing non-deprived smokers, Sakurai and Kanazawa [17] compared smokers with nonsmokers in a variety of memory, calculation and executive function tasks after the smokers had received one or two cigarettes. They found no intergroup differences and suggest that a daily dose of nicotine has little effect on performance. Ernst, Heishman, Spurgeon and London [18] found that smoking history appeared to interact with performance effects in individuals who had been administered nicotine gum, with abstinent smokers performing most poorly and 'never smokers' performing best on a working memory task. Heishman and Henningfield [19] administered nicotine gum across a range of doses to normal nonsmokers both acutely and chronically. Nicotine administration increased the rate of responding and decreased response time, but impaired accuracy on working memory tasks; accuracy also was impaired on visual scanning attention and gross motor coordination.

Functional neuroimaging studies of the effects of nicotine utilizing functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) have suggested that performance enhancement is associated with increased task-induced fronto-parietal-thalamic activation, areas associated with visual attention, arousal and motor activation [20•], or altered lateralization accompanied by reduced cerebral blood flow [21]. A PET study of cerebral glucose metabolism in normal volunteers showed that nicotine administration reduced global glucose metabolism by approximately 10% across most brain regions [22]. Finally, in an intriguing set of studies, Mumenthaler *et al.* [23••] compared the effects of nicotine and the anticholinesterase inhibitor donepezil on the performance of experienced pilots in a flight simulator device. In this highly demanding and stressful cognitive situation, both nicotine and donepezil improved performance substantially with roughly the same effect size, particularly on tasks that required sustained visual attention. Interestingly, a single dose of nicotine improved performance almost as effectively as one month of donepezil administration.

Psychopathological conditions

nAChRs play important roles in the functional impairments of certain neurodegenerative diseases, including AD [24,25]. These associations, although in some cases indirect, are impressive for their longevity and because the associations have been made both by many different investigators and by using more than one approach. The association between AD and nAChRs, although also indirect, suggests that these receptors may mediate important signals that influence the course of the disease. Thus, epidemiological evidence suggests that smokers have a significantly lower incidence of symptoms and diagnosis of AD [26,27]. This inverse relationship even extends to populations with high risk factors for early-onset AD, such as apolipoprotein E gene status [28]. In addition to a strong epidemiological association, many studies have found a decrease in the density of nAChRs in the autopsied brains of AD patients [29–33]. The receptors lost in AD brains are predominantly of the $\alpha4\beta2$ subtype, which binds nicotine and other nicotinic agonists with high affinity and is one of the major nAChR subtypes in mammalian brain [34,35]. This decrease in nAChRs is now well-enough established as part of the findings in autopsied AD brains (>10 studies) that efforts are underway in several laboratories to develop neuroimaging ligands for possible use in early diagnosis or for following the course of the disease [36–42].

Newhouse, Potter, Kelton and Corwin [24] recently reviewed the evidence supporting the importance of nAChRs in the development of AD. In summary, a loss of nicotinic binding sites has been demonstrated in AD patients to be linked to the pathological hallmarks of plaques and tangles. The loss of nAChRs appears to be associated with decreased cerebral perfusion in AD.

Mild cognitive impairment

MCI is defined as a subjective and objective decline in cognition and function that does not meet criteria for a diagnosis of dementia [43–45] and that represents a transitional state between the cognition of normal aging and mild dementia [46]. Furthermore, recent evidence indicates that people with MCI are at high risk for subsequently developing dementia [47,48]. Amnestic MCI [46] appears to represent the condition most likely to progress to AD, whereas individuals who have multiple domains or non-memory domains impaired might progress to AD and/or other types of dementias. By utilizing criteria for amnestic MCI, long-term follow-up studies have suggested that these individuals progress to dementia at a rate of approximately 12% per year [46]. Stimulation of CNS nAChRs with nicotine could be a promising strategy to ameliorate symptoms of MCI and/or slow or prevent progression to frank dementia. In a recent study of cognitive performance in patients with MCI, White and Levin [49] studied 10 subjects with MCI in a double-blind, placebo controlled, crossover study consisting of two four-week periods separated by a two-week washout period. Subjects were given nicotine patches to wear for 16 hours a day up to 10 mg per day. Nicotine significantly improved ratings of overall performance on the clinical global impression scale, as well as objective tests of attentional function on the Connors Continuous performance test and on the neuropsychology test battery, compared with placebo. Intriguingly, nicotine treatment improved the decision-making portion of reaction time to a greater extent than it did the simple psychomotor speed. This was accompanied by improvements in error performance on the Connors Continuous performance test task. Such results are encouraging and have prompted the launching of a NIA-funded multicenter trial to test the efficacy of one year of transdermal nicotine therapy in MCI. In many respects, MCI might be the optimal diagnosis for which to test the efficacy of nicotinic therapy. The likelihood of relatively large numbers of preserved nAChRs and the relative preservation of attentional, acquisition, encoding and retrieval mechanisms, taken together with the evidence for substantial neuroprotective effects of nicotinic stimulation, make MCI an ideal diagnosis to test the efficacy of long-term, low-dose nicotinic stimulation. The large number of controlled efficacy smoking cessation trials in healthy and diseased subjects and their accompanying enormous safety database provide confidence that this treatment will be well-tolerated and safe.

Nicotinic treatment of cognitive impairment in Alzheimer's disease

In clinical studies, Newhouse *et al.* [50] first showed evidence of improved cognitive functioning (decreased errors) following intravenous injection of nicotine in AD subjects. Nicotine administration by subcutaneous injection was then shown to improve attention-related task performance in AD [51,52]. Two weeks of nicotine skin patch treatment was found to significantly improve cognitive function in AD patients by Wilson *et al.* [53]. These investigators found that the major effect of nicotine was to reduce error performance on the new learning phase of the repeated acquisition test — the same parameter on the same task (although performed differently) that Newhouse, Potter, Corwin and Lenox [54] found to be specifically impaired after the nicotinic antagonist mecamylamine. A four-week trial of transdermal nicotine in AD was performed by White and Levin [55], who showed significant improvement in attentional performance, as measured by a continuous performance task, with consistent improvements in omission errors and improved consistency of reaction time. Another nicotine patch study did not find any differential improvement in short-term memory with nicotine compared with placebo [56]. However, there were significant practice effects in that study which could have limited sensitivity. In a unique and not previously reported combination, subjects that were treated with the cholinesterase inhibitor tacrine were administered nicotine; they showed decreased auditory-evoked potential latencies and increased visual-evoked potential amplitude, suggesting improved sensory detection, attention and/or processing [57]. In the only example of treatment with a novel nicotinic agonist, Potter *et al.* [58] showed significant dose-related enhancement of learning and memory in AD patients after acute treatment with the nicotinic agent ABT-418.

In addition to direct stimulation of nAChRs, nicotine might provide cascading effects through stimulation of the release of a variety of transmitters involved in cognitive function, including acetylcholine, dopamine, norepinephrine, serotonin and glutamate [59]. Augmentation of the activities of the remaining nAChRs might provide therapeutic benefit. However, the loss of nAChRs in AD could also limit the potential for nicotinic therapy. This might underlie the lack of nicotine effect in AD seen by Snaedal, Johannesson, Jonson and Gylfadottir [56] and the limitations in the extent of improvement in studies of nicotine in AD. Nicotine treatment might be more effective in older adults with less severe cognitive impairment and more nAChRs, such as those individuals with MCI. The documented neuroprotective effects of nicotine [60,61] could help attenuate this decline.

Effects of chronic nicotine

An important consideration in the development of treatments for cognitive impairment is that they do not lose effectiveness with chronic treatment. It is often the case that chronic administration of agonists causes downregulation of their target receptors and the development of tolerance; this is not the case with nicotine. nAChRs actually show an increase in number with chronic nicotine administration [62,63]. This might be due to the fact that nAChRs have a desensitization response that prevents

chronic overstimulation. However, there might also be downstream accommodations in neural systems that receive nicotinic innervation, which would result in tolerance. Therefore, one cannot make a complete argument on the basis of the known mechanisms of action. Much more convincing are the data that show continuing nicotine-induced cognitive improvement with chronic administration. With mild to moderate AD, nicotine skin patch-induced attentional improvement did not diminish over four weeks of administration [55].

Parkinson's disease

Changes in cholinergic systems in the CNS have also been shown to occur in the brains of patients with PD. In particular, a similar loss of cholinergic cells in the basal forebrain nuclei to that occurring in AD has been described in PD [64]. Studies have shown a marked reduction in cortical nAChR binding that parallels the degree of dementia in PD and increasing age [33,65]. There is similarity between the cortical nicotinic binding site loss in PD and AD, as well as similar changes in other cholinergic markers. The loss of presynaptic [66] cortical nAChRs might reflect degeneration of cortical projections from subcortical structures, notably the nucleus basalis, pedunculo-pontine and lateral-dorsal tegmental nuclei. In PD, loss of striatal nicotine binding appears to occur early but is not associated with a loss of α4 subunit immunoreactivity. Accumulating evidence both in rodents and in primates suggests that α6-containing nAChRs are present on nigrostriatal dopaminergic neurons, and that these receptors may be the most vulnerable to nigrostriatal damage, at least in primates. nAChR ligands that activate this receptor might be particularly useful in PD therapeutics [67••]. Newhouse and colleagues proposed that nicotinic augmentation might be a useful therapeutic strategy for both the motor and cognitive symptoms of PD [68,69].

Several studies have shown that smokers have a lower than expected incidence of PD, suggesting a protective effect of nicotine [70,71]. Tobacco use is associated with greater numbers of dopaminergic neurons in the substantia nigra pars compacta [72].

Nicotine was examined as a treatment for PD as early as the 1920s [73], although these patients suffered from a form of secondary parkinsonism caused by encephalitis lethargica. Some patients in the study showed improvement in rigidity but there were also severe side effects, including seizures, after large doses of nicotine. Fagerström, Pomerleau, Giordani and Stelson [74] reported a detailed study of two patients who had nicotine gum and patch added to their PD therapy. Using a single-subject placebo-control reversal design, improvement was associated with nicotine dosing and involved diminished tremor and disorganized thinking in one patient, and lessened bradykinesia and increased energy in the other. Kelton, Kahn, Conrath and Newhouse [75] examined the acute and chronic effects of nicotine in PD patients over several weeks. Positive effects of nicotine appeared in all motor performance tasks including the pronation/supination task, the stand/walk/sit task and the finger dexterity task. There was a statistically significant improvement on the choice reaction time task in the motor component. Particularly interesting was the persistence of some of the effects of nicotine even several weeks after the cessation of drug administration. These results suggest that nicotine administration has positive effects on certain cognitive and motor aspects of PD, particularly in the area of attention and motor speed. However, a randomized, double-blind placebo-control study of transdermal nicotine added to standard antiparkinsonian therapy for three weeks did not find statistically significant improvements in motor performance on clinical rating scores [19]. In contrast, studies of nicotine gum in PD patients have shown positive effects [76,77].

In addition to nicotine, other novel nicotinic agonists have been examined for effects in PD. SIB-1508 and its racemate, SIB-1765F, are subtype-selective nicotinic agonists particularly to α4β2-containing nAChRs [78]. These compounds appear to have greater efficacy than nicotine at releasing dopamine from striatal slices. SIB-1765F potentiated the positive locomotor effects of L-dopa in a reserpine model of PD in rats [79] with a rapid onset of action. The compound produced a small improvement in locomotion when administered alone; however, the effect was much greater when combined with L-dopa. SIB-1508Y, an isomer of SIB-1765F, was more potent in this model and has also shown positive activity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkey model of PD [80]. A dose of SIB-1508Y which was inactive by itself caused significant improvement in cognition and motor aspects of task performance when administered simultaneously with L-dopa.

Schizophrenia

Research in normal smokers and in patients with schizophrenia has indicated that cigarette smoking or nicotine administration may improve cognitive functioning, including memory, attention and spatial perception [81]. Epidemiological studies have shown a higher rate of smoking among schizophrenic patients (90%) compared with the general population (20–30%), and a lower rate of smoking cessation among schizophrenic patients [82]. It has been hypothesized that the high rate of smoking among schizophrenic patients might result, in part, from the ability of nicotine to ameliorate some of the cognitive deficits associated with schizophrenia [83].

Schizophrenic patients exhibit an auditory sensory gating deficit characterized by diminished suppression of P50 auditory-evoked response to repeated stimuli. Nicotine

transiently corrects the diminished gating response of P50 auditory-evoked potential in schizophrenic patients and their non-smoking relatives [84]. Clozapine, but not typical antidopaminergic antipsychotic drugs, improves gating of the P50-evoked response [85], and it has been suggested that modulation of smoking by clozapine treatment may, in part, be caused by similar mechanisms. The fact that these attentional abnormalities also occur in non-psychotic relatives of schizophrenic patients suggests a genetic basis for this deficit. The P50 inhibition deficit in schizophrenia has been linked to chromosome 15q13–14 in the region of the α7 subunit gene [86]. Postmortem studies have shown a reduction in the number of α-bungarotoxin-sensitive (α7-containing) nAChRs in the hippocampal region of schizophrenic patients [87], which appear to be secondary to polymorphisms in the α7 promotor [88•]. Another form of cognitive deficit associated with schizophrenia is latent inhibition, in which pre-exposure to a stimulus inhibits conditioning to that stimulus [89]. It has been suggested that smokers have enhanced latent inhibition, which is dependent upon the pre-exposure parameters [90].

Schizophrenic patients have impairments in other cognitive domains, including deficits in visuospatial working memory (VSWM), which is partly mediated by dopamine in the prefrontal cortex. Smoking abstinence differentially alters VSWM in schizophrenic versus control smokers, and cigarette smoking has beneficial effects on VSWM in schizophrenic, but not control, smokers [91]. Higher doses of nicotine patch improved reaction time, but not accuracy, in a spatial rotation task, and also improved performance on a visual-match-to-sample task in schizophrenic patients treated with haloperidol [92]. Recently, Smith, Singh, Infante, Khandat and Kloos [93•] have shown increased performance on two-choice reaction time, spatial rotation (accuracy/reaction time) and visual-match-to-sample tasks from the automated neuropsychological assessment battery (ANAM) with both high and denicotinized cigarettes in schizophrenic patients. Active nicotine nasal spray improved accuracy on a spatial organization task, and tended to improve some measures of verbal memory (paired words and short story from Randt memory test) and two-choice reaction time in schizophrenic patients. The differences in results between the above mentioned studies might be caused by different forms of smoking and/or to the fact that most of the patients in the Smith study [93•] were on atypical antipsychotic medications.

Attention deficit/hyperactivity disorder

Adults and adolescents who are diagnosed with ADHD smoke at significantly higher rates than comparable people in a community sample, and have lower quit ratios (percentage of ever-smokers who are ex-smokers) than the general population (23% versus 51.6%) [94]. In this study, there was a relationship between current smoking status and retrospective reports of ADHD symptoms, with current smokers recalling a greater number and greater severity of ADHD symptoms in childhood. A prospective study of tobacco smoking and substance dependence [95] found that, by age 17, 46% of adolescents with ADHD were smoking cigarettes daily compared with 24% of age-mate controls. This finding continued into adulthood where 35% of adult subjects with ADHD were smokers as compared with 16% of age-matched controls. These findings raise the possibility that adolescents with ADHD may be using cigarette smoking to relieve some of the symptoms of ADHD.

There is an emerging body of literature examining the therapeutic effects of nicotinic stimulation on the symptoms of ADHD. Levin *et al.* [96] studied the acute effects of transdermal nicotine and placebo in adults with ADHD (both smokers and non-smokers). They reported significant improvements in self-rated vigor and concentration and observer-rated illness severity for both subject groups (i.e. smokers and non-smokers). In addition, they found improvements in speed of responding for both the smokers and non-smokers, and a reduction in variability of reaction time for the smokers. In a second study, Levin, Conners, Siliva, Canu and March [97] studied the effects of chronic (four week) nicotine administration compared with methylphenidate treatment, placebo treatment and a combination of nicotine and methylphenidate in 40 adults with ADHD. They found nicotine to significantly reduce clinician ratings of severity of symptoms, and to decrease self-reported symptoms of depression. They found sustained improvement in the variability of reaction times on a continuous performance task. Wilens *et al.* [98] studied a novel cholinergic channel activator (nicotinic agonist), ABT-418, in 32 adults with ADHD for treatment of their symptoms. This study employed a crossover design with each subject receiving two double-blind three-week treatment periods with placebo and ABT-418. Significant improvements in subjective ratings of attentiveness and observer-rated illness severity on a clinical global impressions scale were seen following treatment with ABT-418.

The cognitive deficits in attention in ADHD are not in the areas of information processing or in perceiving information, but are seen in motor inhibition, motor control and in anticipating events [99,100]. Current views of ADHD hold failures of cognitive/behavioral inhibition as the central deficit of this disorder [101]. Potter and Newhouse [102] have recently examined changes in behavioral inhibition following nicotine administration to eight non-smoking adolescents with ADHD. In this study, subjects were administered acute transdermal nicotine (7 mg for 60 min), oral methylphenidate or placebo on three separate study days. Nicotine was associated with significant improvements in stop signal reaction time (a measure of the speed of inhibition). This

effect was comparable to the size of change seen after a single dose of oral methylphenidate and was not associated with general improvements in performance on this task, as overall speed and accuracy were not different from placebo. This study also found improved cognitive/behavioral inhibition associated with nicotine administration on the Stroop task, with a smaller Stroop effect (the cost of inhibiting) following nicotine, but not methylphenidate or placebo, treatment. In addition, nicotine was associated with decreased subject ratings of irritability and observer ratings of anxiety.

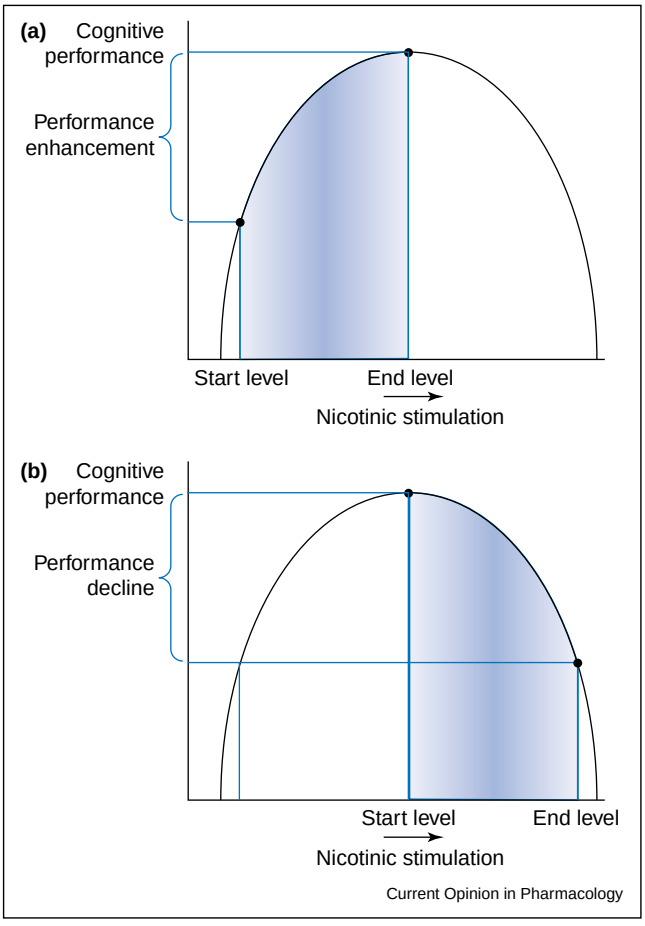
These initial studies indicate that nicotinic treatment may be useful for the symptoms of ADHD. The well-known effects of nicotine on attention might include positive effects on cognitive/behavioral inhibition, which is the core cognitive deficit of ADHD. Current standard pharmacological treatment for ADHD consists mainly of psychostimulants (e.g. methylphenidate), which are presumed effective via their effects on dopamine. Nicotine has been shown to increase the release of several neurotransmitters, including dopamine [103]. nAChRs might serve to regulate dopamine release in both striatal and mesocortical pathways [104,105]. Levin, McGurk, Rose and Butcher [106] have performed an extensive series of studies suggesting complex interactions with several possible anatomical loci for the site(s) of interaction, including both limbic and hippocampal areas, as well as descending projections to dopamine-containing areas of the mesencephalon via the medial habenula. Thus, is it possible that nicotine is exerting positive effects on inhibition and sustained attention in ADHD by enhancing the dopaminergic tone of both the striatal-frontal and mesocortical dopaminergic systems. In support of this conclusion, Solanto [107] in a recent review concluded that the majority of cognitive symptoms of ADHD (including behavioral inhibition) is mediated by the prefrontal cortex, and that stimulant medication might affect cognition by acting at D1 and D2 receptor sites to optimize the neurochemical environment.

Does nicotinic stimulation enhance cognitive functioning or performance?

A review of the recently published works on the effects of nicotine on cognitive function and performance in humans could lead to some confusion because of the contradictory conclusions of these studies. There seems to be an almost equal number of studies that show either performance enhancement or impairment by nicotine. A careful look at the nature of these disparate studies reveals clues to understanding the seemingly contradictory nature of research in this area.

Studies that tend to show impairment generally use normal non- or never-smokers as subjects, even studies with chronic use. These studies tend to conclude that nicotine does not improve cognitive functioning and most often impairs it. In contrast, studies that tend to show improvement generally utilize smokers or clinical populations of subjects. These studies generally demonstrate and/or conclude that nicotine has cognitive-enhancing effects. These disparate results can be resolved by considering that the findings reflect the differing populations utilized for the experiments. These populations can be expected to show quite different responses to nicotine from the principles of rate dependency or baseline effects [108] of nicotine (e.g. the Yerkes-Dodson principal). This is illustrated in Figure 1. Cognitive performance can be

Figure 1



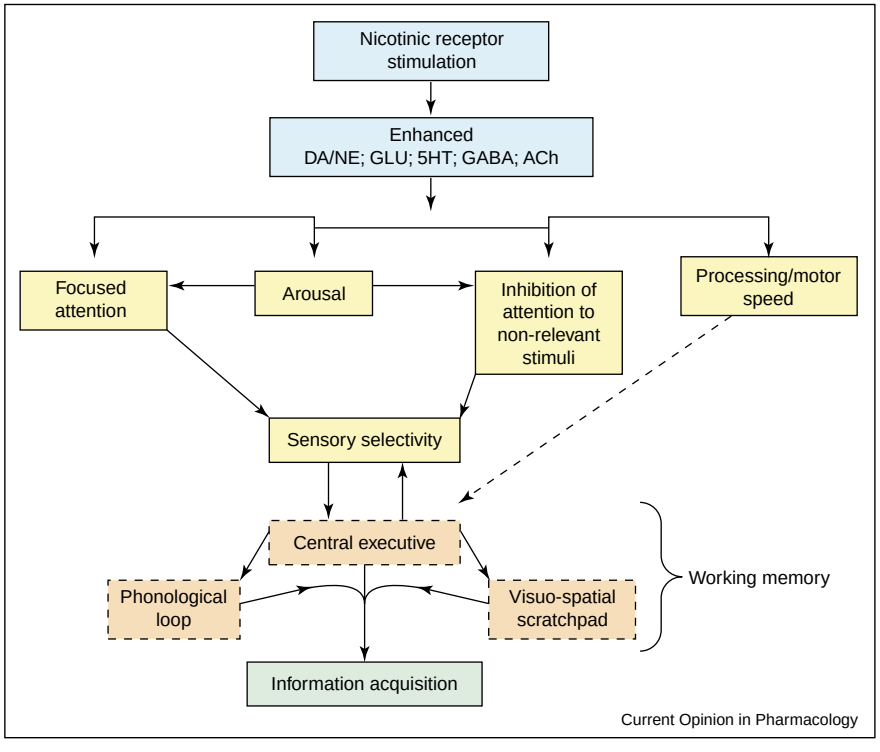
This figure illustrates two situations in which an equivalent degree of nicotinic stimulation produces opposite effects and illustrates the general principle that the results of nicotinic stimulation are a reflection of baseline performance level. The results of nicotinic stimulation, like many biological systems, can either increase or impair function (Yerkes-Dodson principal). **(a)** Illustrates an example of an individual whose cognitive performance is impaired or for whom task demands do not match the level of ongoing nicotinic stimulation. The nicotine administration or nicotinic receptor stimulation produces an improvement in cognitive performance, bringing performance to near optimal levels. **(b)** Illustrates a different scenario where the individual performance is already at or near optimum levels. In this case, the same degree of nicotinic stimulation as in **(a)** produces impairment of performance. This illustration might help to explain apparently paradoxical results of cognitive studies in differing populations.

envisioned as a curvilinear function related to nicotinic stimulation, with intermediate levels of stimulation producing optimal performance and either low or high levels of stimulation impairing performance. If an individual subject is performing suboptimally because of a disease state or impairment (e.g. AD), his performance will be enhanced by increased nicotinic stimulation (Figure 1a). However, if an individual subject is already performing at or near their optimal level of performance, increasing nicotinic stimulation will produce deterioration in cognitive functioning (Figure 1b). The same analysis can apply if the individual is normal but the task demands are severe. If the task is demanding enough in terms of attention, especially over a period of time, then the individual might move back to the left in terms of the performance curve, and optimal performance will require enhanced nicotinic stimulation.

Studies of normal volunteers, especially non- or never-smokers, are unlikely to show cognitive improvement with nicotinic stimulation because of the fact that these individuals are likely to be operating at or near their optimal level of performance, particularly in the setting of experimental paradigms with, for example, pre-training for cognitive tasks and financial rewards for participation. In addition, this might reflect differences between non-smokers and smokers in the underlying neurobiology and/or efficiency of the nicotinic system, and suggests that some of the reasons why subjects smoke may be, in part, related to the degree of improvement in cognitive performance that is seen with nicotinic stimulation.

The preponderance of evidence suggests that stimulation of nAChRs is most easily detected by effects on attentional systems and, to some extent, psychomotor speed. The most well-documented effect of nicotine is intensifying or sustaining attention to stimuli or tasks over a prolonged period of time. In addition, there is evidence from studies of individuals with disorders such as schizophrenia and ADHD that nicotinic stimulation enhances selective attention, sensory detection and inhibitional processes in attention. Positive effects of nicotine on learning or memory might be mediated by its effects on attentional functioning (Figure 2). Learning and memory require acquisition, encoding, storage and retrieval; however, attention is the 'front end' of this process, and adequate attentional functioning is a primary requirement.

Figure 2



Proposed model for nicotinic receptor stimulation effects on neurotransmitter function and attentional function. In this model, nAChR stimulation is presumed to lead to enhanced neurotransmitter release in particular brain areas relevant to arousal, sustained attention, inhibitional processes and processing/motor speed. Sensory selectivity is conceptualized as being secondary to improved attentional performance. These processes are thought to impinge on the 'central executive' component of Baddeley's model [110] for working memory leading to improved acquisition of information.

Conclusion: attention as a nicotinic endophenotype

In summarizing research done on nicotine and cognition, Warburton and Rusted [109] concluded that the most robust effects of nicotine are seen in tasks that have a high attentional requirement (i.e. memory enhancement might be a consequence of improved attentional functioning). Attention and related processes can be thought of as an endophenotype for nicotinic stimulation and consequently drug development. Attention, central processing impairment and executive dysfunction might be orthogonal to the underlying neuropsychiatric diagnosis and should be considered as an independent target for nicotinic drug development across diagnostic categories. Particular attentional deficits in different diagnoses could still respond to nicotinic stimulation; however, the parameters for assessing improvement might be quite different between disease states and will require careful attention to receptor subtype-specific agents, dosing regimens and outcome measures in clinical trials. Paying careful attention to the issue of baseline-dependency in treatment response will be vital to ensure appropriate interpretation of experimental results, both for studies of normal individuals and for those with disease states. Targeting specific populations that are already impaired is much more likely to reveal potential benefits of nicotinic stimulation. Studies of normal or unimpaired individuals with nicotinic drugs are unlikely to show cognitive benefit except under extreme task demands.

Acknowledgements

Preparation of this work and/or research described was supported in part by NIMH R29-46625, GCRC M01-00109, NIA R01 AG022462-01, Abbott Laboratories and SIBIA Neurosciences.

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- • of special interest
- •• of outstanding interest

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