Published in final edited form as:

Biochem Pharmacol. 2013 October 15; 86(8): 1145–1152. doi:10.1016/j.bcp.2013.07.021.

Complex Relationships of Nicotinic Receptor Actions and Cognitive Functions

Edward D. Levin, Ph.D.

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center

Abstract

Nicotine has been shown in a variety of studies to improve cognitive function including learning, memory and attention. Nicotine both stimulates and desensitizes nicotinic receptors, thus acting both as an agonist and a net antagonist. The relative roles of these two actions for nicotine-induced cognitive improvement have not yet been fully determined. We and others have found that acute nicotinic antagonist treatment can improve learning and attention. Nicotine acts on a variety of nicotinic receptor subtypes. The relative role and interactions of neuronal nicotinic receptor subtypes for cognition also needs to be better characterized. Nicotine acts on nicotinic receptors in a wide variety of brain areas. The role of some of these areas such as the hippocampus has been relatively well studied but other area like the thalamus, which has the densest nicotinic receptor concentration are still only partially characterized. In a series of studies we characterized nicotinic receptor actions, anatomic localization and circuit interactions, which are critical to nicotine effects on the cognitive functions of learning, memory and attention. The relative role of increases and decreases in nicotinic receptor activation by nicotine were determined in regionally specific studies of the hippocampus, the amygdala, the frontal cortex and the mediodorsal thalamic nucleus with local infusions of antagonists of nicotinic receptor subtypes ($\alpha 7$ and $\alpha 4\beta 2$). The understanding of the functional neural bases of cognitive function is fundamental to the more effective development of nicotinic drugs for treating cognitive dysfunction.

Keywords

Nicotinic; Cognition; Antagonist; Desensitization

1. Introduction

Neuronal nicotinic receptors play a critical role in memory function in both humans and experimental animals. Nicotine has long been known to produce significant improvements in attention, learning and memory function [1]. Nicotinic treatments have shown promise for providing a novel avenue of treatment for syndromes of cognitive dysfunction such as Alzheimer's disease, mild cognitive impairment (MCI) and attention deficit hyperactivity disorder (ADHD) as well as the cognitive deficits in other syndromes such as schizophrenia and Parkinson's disease [2–4]. It is important to understand the receptor actions by which nicotinic drugs affect cognitive functions both to improve our basic understanding of the

© 2013 Elsevier Inc. All rights reserved.

Address Correspondence to: Edward D. Levin, Ph.D., Duke University Medical Center Department of Psychiatry and Behavioral Sciences, Box 104790 DUMC, Durham, NC 27710, USA, Phone: 1-919-681-6273; Fax: 1-919-681-3416, edlevin@duke.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

roles nicotinic receptor actions play in cognitive function and to improve our development of nicotinic therapeutic drug treatments to counteract cognitive dysfunction.

Classically, it was thought that only the receptor stimulatory effects of nicotine and other nicotinic agonists were important mechanisms for cognitive improvement. However, given that nicotinic receptors are quite easily desensitized and that nicotinic agonists are also desensitizing agents [5, 6], the relative roles of nicotinic agonist effects vs. net antagonist effects by desensitization for cognitive improvement are not clear. Desensitization of nicotinic receptors has been suggested as a useful avenue for drug development [7, 8]. Nicotinic receptor desensitization shares some attributes to nicotinic receptor blockade with antagonist treatment. Both desensitization and antagonism serve to decrease net activation of nicotinic receptors. Conformational changes of nicotinic receptors that decrease its responsivity to be activated is the central nature of a desensitizing effect; whereas the simple occupation of the recognition site of the receptor site without activation is the hallmark of the antagonist effect. The degree to which nicotinic receptor desensitization outlasts the presence of the desensitizing drug on the receptor is still under study.

One critical factor is the great diversity of location of nicotinic receptors throughout the brain. Nicotinic receptors in different brain regions are likely to play different roles in cognitive function. We have found with local infusion studies regional heterogeneity for nicotinic involvement in memory function. The differential role in cognition played by nicotinic receptors in different brain areas is important not only for a better basic understanding of the complex of neural systems involved in nicotinic components of cognitive function, but also for development of effective clinical therapeutics. When nicotinic drugs are administered systemically they have effects throughout the brain, on receptors in areas, which improve cognitive function, as well as those in other areas, which diminish cognitive function. Regionally selective loss of nicotinic receptors in neurodegenerative disorders can alter the balance of these nicotinic drug effects throughout the brain. The effects of systemic nicotine administration has been shown in our studies to be altered by local infusion of nicotinic antagonists and selective lesions as reviewed below.

2. Clinical Importance

Human studies have demonstrated positive effects of nicotine on cognitive function [1, 9, 10]. The issue concerning whether nicotine can improve cognitive function in normal nonsmokers who have no pre-existing attentional impairment has been addressed. Adult nonsmokers without ADHD symptoms or other symptoms of cognitive impairment were administered 7 mg/kg/day nicotine patches and placebo [11]. Nicotine significantly reduced the number of errors of omission on the continuous performance task (CPT). No change in errors of commission was found so the nicotine induced improvement in performance was not merely due to an increase in overall response rate. It was also found that the nicotine patch significantly decreased response time variability. That is, nicotine increased consistency of response. As reviewed below nicotine treatment also improves cognitive function in people who are not smokers but have conditions of cognitive impairment.

Selective effects of nicotine on attentional processes have also been studied in smokers [12]. 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 tests of attentional function as well as the Stroop test. It was shown that the 6 h, 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. The authors suggested that nicotine mainly improves the intensity features of attention, rather than the selectivity features [12]. Nicotine-induced attentional

improvement has also been found in MRI imaging studies to be accompanied by increased activation in the parietal cortex, thalamus and caudate [13]. Kumari et al. [14] found that nicotine induced improvements in memory were accompanied by increases in activity in frontal cortical regions of the brain.

Nicotinic treatments have shown promise for improving cognitive function in a variety of conditions from Alzheimer's disease to mild cognitive impairment, schizophrenia and attention deficit hyperactivity disorder [1, 15–17]. Alzheimer's disease is characterized by a substantial decline in nicotinic acetylcholine receptors [18] and the extent of nicotinic receptor loss in brain regions important for cognitive function such as the hippocampus and frontal cortex is related to the degree of cognitive impairment in Alzheimer's disease [19, 20]. Nicotinic receptor acting drugs are a promising avenue being developed for treatment of the cognitive impairment of Alzheimer's disease [16]. We have found that nicotine skin patch treatment significantly improved attentional function in people with mild to moderate Alzheimer's disease [21]. In a recent six-month double blind, placebo controlled study it was found that people with mild cognitive impairment showed significant improves in attention and memory with chronic nicotine skin patch treatment [17]. A clinical trial with EVP-6124 a selective $\alpha 7$ partial agonist from Envivo Pharmaceuticals found a significantly improved cognitive function in people with Alzheimer's disease [22]. In a six-month, double blind, placebo-controlled trial over four hundred patients were enrolled and three doses of EVP-6124 were tested in patients with mild to moderate Alzheimer's disease. EVP-6124 at 2 mg per day for 23 weeks significantly improved the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog-13) and the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB).

Schizophrenia was once considered to be primarily a psychotic disorder, but it has become apparent that schizophrenia is also a syndrome of substantial cognitive impairment [23, 24]. Cognitive dysfunction in schizophrenia ranges from impaired sensory gating to deficits in attentional and other higher order cognitive function. There is a decrease in nicotinic receptor concentration in the brains of people with schizophrenia [25]. Deficits in learning, memory and attention compromise the ability of people with schizophrenia to function adequately in everyday activities and to successfully reintegrate into society. Antipsychotic drugs can effectively combat hallucinations, but often are ineffective in treating cognitive impairment and can exacerbate the dysfunction [26, 27]. Clearly, better medications to improve cognitive function in schizophrenia are necessary [28, 29]. A variety of approaches for treating these cognitive impairments has been tried; especially promising are nicotinic agonists, including selective $\alpha 7$ nicotinic agonists [30, 31]. For the efficient development of novel nicotinic treatments for cognitive impairment it is important to know the critical mechanisms of action for nicotinic involvement in cognitive function for reversing or improving cognitive dysfunction.

Adults with ADHD were found in our study to show significantly improved attentional performance when administered nicotine skin patches either acutely [32] or chronically for four weeks [33]. Nicotine also improves behavioral inhibition in adolescents with ADHD [34]. People with ADHD also have shown improved attentional performance with nicotine treatment. The more selective nicotinic $\alpha 4 \beta 2$ agonist ABT-418 was found to improve attentional symptoms of in adults with ADHD [35]. Interestingly, Potter et al. [36] found that low doses of the nicotinic antagonist significantly improved memory in adults with ADHD. It may be the case that modest blockade of nicotinic receptors can improve cognitive function. Since nicotine desensitizes nicotinic receptors and thus has some net antagonistic actions, might it be that some of nicotine induced cognitive improvement is due to this desensitization?

3. Experimental Preclinical Studies

Memory in the radial-arm maze is significantly improved by nicotine in rats [1]. Nicotine was also found to reverse haloperidol-induced memory impairments [37]. To further nicotinic drug development and to provide a better understanding of the basic neural mechanisms of memory, it is important to determine the critical neural structures and nicotinic receptor subtypes necessary for nicotine-induced memory improvement. Our studies have shown involvement of $\alpha 4 \beta 2$ and $\alpha 7$ nicotinic receptors in the hippocampus as being particularly important for working memory function. Infusions of nicotinic $\alpha 4 \beta 2$ and $\alpha 7$ nicotinic antagonists cause working memory impairments [38]. Memory has been found in a variety of studies to have nicotinic acetylcholine receptors as a critical neural substrate (for review see [1]). We have conducted a series of studies over the past two decades to determine the specific brain areas and receptor subtypes involved in nicotinic receptor involvement in memory. Acute and chronic systemic nicotine administration significantly improves working memory function on the radial-arm maze and reverses the amnesic effects of the NMDA glutamate antagonist dizocilpine. The $\alpha 4 \beta 2$ nicotinic agonist metanicotine (RJR 2403) significantly improved working memory function in rats on the 8-arm radial maze. Interestingly, this effect was evident both one-hour after perioral administration as well as six hours after dosing, long after the compound had been catabolized indicating a persistent effect of nicotinic stimulation [39].

Using another test of rodent memory function using the elevated plus maze Kruk-Sloma and colleagues [40] also found in mice that nicotine improves memory function an effect blocked by the nicotinic antagonist mecamylamine. Interestingly, they found that low to moderate doses of mecamylamine also significantly attenuated the memory impairment caused by the muscarinic cholinergic antagonist scopolamine. This supports other findings reviewed below that nicotinic antagonist administration can in some cases improve cognitive function.

Attention is also improved by nicotine in experimental animals [41–44]. Using an operant visual signal detection task, it has been demonstrated that a low dose range of nicotine (0.025–0.05 mg/kg) increased hit and percent correct rejection supporting an improvement in attention [42, 43, 45]. In the same procedure the higher doses of nicotinic antagonist mecamylamine decreased choice accuracy by reducing both percent hit and percent correct rejection [46]. Mecamylamine in the upper dose range has been shown also to impair attentional performance in another well-validated rodent model of attention, the five choice serial reaction time task [47]. Using the same task, Ruotsalainen et al. reported a decrement only in reaction time, not accuracy with mecamylamine in rats. The cognitive impairing effects of mecamylamine suggest the involvement of the neuronal nicotinic cholinergic system in normal cognitive functioning [48]. Research into the effects of low doses of mecamylamine with regard to attentional function remains to be done. The $\alpha 4 \beta 2$ nicotinic agonist ABT-418 has also been shown to improve accuracy in the attention signal detection task [49]. Terry et al. found that the nicotinic agonist SIB-1553A with specificity for $\alpha 4$ subunit containing nicotinic receptors significantly improves performance of rats on a 5-choice attentional task, but only when accuracy was reduced behaviorally with a distracting stimulus, or pharmacologically by the NMDA-selective glutamate receptor antagonist dizocilpine [50]. Nicotine has also been shown to reverse attentional impairments in rats caused by basal forebrain lesions [44, 51] or lesions of the septohippocampal pathways [52]. Interestingly, chronic nicotine infusion has been shown to significantly diminish the impairing effects of the typical antipsychotic drug haloperidol and atypical antipsychotic drugs, clozapine and risperidone [53] on attentional performance in female rats using an operant visual signal detection task.

Nicotine is effective in reversing the attentional impairment caused by the NMDA glutamate antagonist dizocilpine [42, 43] (Fig. 1). In a series of studies rats were trained to assess attention in visual signal detection operant task, memory on the win-shift radial-arm maze and learning on a repeated acquisition procedure on the radial-arm maze. The nicotinic receptor desensitizing and antagonist drugs were administered to determine the effects of decreasing nicotinic receptor activity on cognitive function. We found that nicotinic receptor desensitization or outright blockade can significantly improve attention, learning and memory. In rats trained on the operant visual signal detection test of attentional function, the

4 2 nicotinic receptor desensitizing agent sazetidine-A significantly improved attentional function, reversing attentional impairment caused by blockade of muscarinic cholinergic with scopolamine and blockade of NMDA glutamate receptors with dizocilpine (Fig. 2) [54]. Recently, we have found that administration of the 4 2 nicotinic antagonist DH E also significantly improves attention in the same operant visual signal detection test, reversing the impairment caused by dizocilpine. Sazetidine-A, a selective 4 2 nicotinic receptor desensitizing agent, reversed the attentional impairments caused by either NMDA glutamate blockade with dizocilpine or muscarinic cholinergic blockade with scopolamine [54]. Sazetidine-A also has some partial agonist, so it was unclear to what degree the therapeutic effect derived from its desensitizing effect vs. its partial agonist effect (but the agonistic effect is very short lasting while desensitization is prolonged). Most recently, we have found that the 4 2 nicotinic receptor antagonist DH E effectively attenuates dizocilpine-induced attentional impairment (Fig. 3) [55] showing that an outright antagonist can have a similar beneficial effect on attention. 7 agonist treatment was also found in our studies to significantly improve attentional function in the signal detection task [56]. We also found that the 7 antagonist MLA effectively attenuated attentional impairment (Fig. 4) [55], suggesting that it might be the net desensitization of 7 nicotinic receptors that may underlie attentional improvement with 7 ligand administration.

Learning was studied in the repeated acquisition procedure in the radial-arm maze. A low dose of the non-specific nicotinic antagonist mecamylamine was found in our studies to significantly improve learning and memory in the radial-arm maze [57]. Learning was also improved by the 7 nicotinic full agonist ARR-17779 in the repeated acquisition task in the radial-arm maze in which a new problem is presented each session [58]. On this same task, nicotine did not improve accuracy whereas the mixed nicotinic agonist/antagonist lobeline did significantly improved accuracy [59]. Perhaps the more specific 7 effects of ARR-17779 (receptors which are very readily desensitized) and the partial antagonist effects of lobeline may contribute to their greater efficacy on the repeated acquisition task.

Anatomic Studies

With a series of local infusion studies we have begun characterizing the anatomic circuits by which nicotinic receptors are involved in cognitive function. We have investigated nicotinic 7 and 4 2 receptors in working memory as measured in the radial-arm maze.

Limbic system nicotinic receptors in particular those in the hippocampus have been shown in our previous studies to play important roles in working memory. We showed that blockade of 7 and 4 2 nicotinic receptors in the ventral or dorsal hippocampus [60–65] with MLA and DH E caused significant working memory impairments in the radial-arm maze. Interestingly, effects of 7 and 4 2 nicotinic blockade were not additive in the hippocampus. In the basolateral amygdala blockade of 7 and 4 2 nicotinic receptors also caused memory impairments [66]. In this area 7 and 4 2 antagonists reversed each other's impairments indicating that nicotinic receptors in this area have complex effects on circuitry in the amygdala, which remains to be fully understood.

The thalamus and habenula have the greatest density of nicotinic receptors [67]. The epithalamic structure the habenula has very dense nicotine innervation and relays connections from the telencephalon to the brainstem. Chronic habenular infusions of the nicotinic antagonist mecamylamine caused memory deficits [68]. This was reversed by systemic nicotine administration. Thalamic nicotinic receptors play a variety of roles in working memory. The mediodorsal thalamic nucleus has direct connections with the frontal cortex. Infusion of the $\alpha 4 \beta 2$ nicotinic antagonist DH β E into this area either acutely or chronically significantly improved memory in rats. Acute MLA infusion into the mediodorsal thalamic nucleus did not affect memory by itself, but it did reverse the improvement caused by DH β E [69]. Chronic systemic nicotine administration reversed the beneficial effect of DH β E infusions into the MD.

The cortex, brainstem and other brain regions with nicotinic receptors that are relevant to memory function have also been investigated in our studies. The role of frontal cortical nicotinic receptors in working memory function was studied in relationship to response to the antipsychotic drug clozapine. Frontal cortical infusions of the $\alpha 4 \beta 2$ nicotinic antagonist DH β E significantly potentiated the memory [70]. This contrasts to the interaction of DH β E infusions into the hippocampus and systemic clozapine, where clozapine significantly attenuated the memory impairment caused by blockade of hippocampal $\alpha 4 \beta 2$ receptors [65]. Local infusion of the nicotinic antagonist mecamylamine into the brainstem dopaminergic nuclei the ventral tegmental area (VTA) and substantia nigra significantly impaired working memory performance in the radial-arm maze [71]. Nicotinic antagonist infusions into the superior colliculus (unpublished data) or nucleus accumbens [72] were not found in our studies to significantly effect working memory performance on the radial-arm maze.

4. Issues to Be Resolved

The relative roles of nicotinic stimulation vs. desensitization in cognitive function are not well understood. Nicotine, is the prototypic agonist of nicotinic receptors, however, stimulation is not nicotine's only action. It also potently desensitizes nicotinic receptors. Desensitization is an inherent property of nicotinic receptors. Nicotinic receptor activation is followed by a period of desensitization during which it cannot be activated by either the endogenous ligand acetylcholine or exogenous drug ligands like nicotine and other nicotinic agonists. Therefore, every nicotinic agonist is also a desensitizing agent. Desensitization is not merely the cessation of an agonist effect; it has physiological consequences of its own through a more prolonged limitation of the actions of acetylcholine. The degree to which agonist or desensitizing effects of nicotinic agonists contribute to their pharmacodynamic effects is currently poorly understood. Classically, it was thought that the cognitive enhancing effects of nicotine was due to its receptor stimulation and that receptor desensitization only diminished the efficacy of nicotine or other nicotinic agonists.

The centrality of the nicotinic stimulatory effect of nicotine for its cognitive enhancing effects was reinforced by findings that co-administration of a nicotinic antagonist would diminish the improvement caused by the agonist. However, this ignores the inverted U-shaped dose-effect curves seen with cognitive enhancing drugs and in particular nicotinic agonists. Apparent blockade of the nicotinic agonist effect of cognition with the corresponding antagonist may not be as simple as first appears. The experiments showing reversal of nicotinic agonist effects with antagonist co-administration are most usually carried out using the dose of agonist that produces the peak effect. For example, Thomsen et al. demonstrated a beneficial cognitive effect of the nicotinic $\alpha 7$ agonist SSR180711 with an inverted U-shaped dose-effect function reversing the adverse effects of NMDA glutamate blockade with PCP [73]. In a follow-up experiment, they showed that the beneficial action of the most effective SSR180711 dose was reversed with the $\alpha 7$ antagonist MLA. This

result could be explained as discussed in the article that MLA blocked the agonist effect of SSR180711. However, another explanation is that SSR180711 may have its beneficial action expressed via desensitization and net antagonist effect on $\alpha 7$ receptors. The additional antagonist action provided the MLA may have extended the $\alpha 7$ underactivity past the optimal level down the higher end of the inverted U-shaped dose-effect curve. Without conducting a detailed study of the dose effect functions of interactions between nicotinic agonists and antagonists, one cannot be sure if the antagonist reverses the agonist effect or extends the net antagonist effect of desensitization with the addition of a blocker such that the extent of decreased stimulation exceeds the therapeutic range.

We found that sazetidine-A, a nicotinic $\alpha 4 \beta 2$ receptor desensitizing agent, to significantly improve attentional function in terms of reversing attentional impairments caused by the NMDA glutamate antagonist dizocilpine (MK-801) and the muscarinic cholinergic antagonist scopolamine [54, 74]. However, sazetidine-A also has an agonist effect at one of the configurations of $\alpha 4 \beta 2$ receptors [75], leaving open the possibility that it may have been this agonist effect rather than the net antagonist effect from desensitization that was responsible for the attentional improvement.

To examine the effect of only decreasing $\alpha 4 \beta 2$ receptors, we tested the effect of DH β E in reversing dizocilpine-induced attentional impairment. As shown in the preliminary studies section DH β E did attenuate the attentional impairment in a way that resembles the reversal of dizocilpine by the $\alpha 4 \beta 2$ desensitizing agent sazetidine-A on the same visual signal detection task [55]. For comparison the effect of $\alpha 7$ nicotinic receptor blockade with MLA was assessed. Since $\alpha 7$ nicotinic receptors are easily desensitized it may be the case that some of the beneficial effects of $\alpha 7$ nicotinic agonists may derive from the net desensitization of $\alpha 7$ nicotinic receptors

Attention is not the only cognitive function to be improved by nicotinic antagonist treatment. We have also found that low doses of the nicotinic antagonist mecamylamine can improve learning [57] and memory [76]. Others have also found instances of nicotinic antagonist induced cognitive improvement. Picciotto and Buccafusco both concluded that net decreases in nicotinic stimulation could provide clinically beneficial effects including cognitive improvement [7, 8]. In a clinical study low doses of mecamylamine were also been found to significantly improve memory in adults with ADHD [36].

Differential and interactive roles of $\alpha 4 \beta 2$ and $\alpha 7$ nicotinic receptors with regard to cognitive function need to be more fully understood. Both nicotinic $\alpha 4 \beta 2$ and $\alpha 7$ receptor subtypes have been found to be involved in cognitive function. Selective agonists of both receptor subtypes have been shown to improve attention and memory function. The differential roles of $\alpha 4 \beta 2$ and $\alpha 7$ receptors in cognitive has yet to be fully understood. Local infusion studies have shown that their effects are not additive and in some cases mutually antagonistic. In the hippocampus both MLA and DH β E impair working memory but the combined effects are not additive [63]. In the basolateral amygdala, MLA and DH β E counteract each other's effects [66].

Nicotinic receptors in different brain areas play different roles in cognitive function. Local brain infusion studies have demonstrated the regional heterogeneity of nicotinic receptor involvement in cognitive function. Ventral or dorsal hippocampal infusions of nicotinic $\alpha 4 \beta 2$ and $\alpha 7$ antagonists DH β E and MLA cause working memory impairments. The specific brain systems underlying the nicotine antagonist-induced cognitive improvement are still not well understood. There is evidence pointing to the importance of mediodorsal thalamic nucleus, which has direct connections with the frontal cortex. In an earlier set of studies we found that administration of the $\alpha 4 \beta 2$ antagonist DH β E directly into the mediodorsal

thalamic nucleus either acutely or chronically significantly improved working memory function [69]. This contrasts with acute and chronic DH E-induced memory impairment with infusion in the ventral hippocampus [62, 63].

This regional heterogeneity of nicotinic involvement in cognitive function is likely to play an important role in the effects of systemically administered nicotinic drugs, particularly in different neuropathological conditions with differential nicotinic receptor loss in specific neuroanatomical areas. This can be seen in experimental animal models of specific regional damage altering systemic nicotine effects. Chronic systemic nicotine infusion causes improvement in working memory when the regional distribution of nicotinic receptors is normal [77] and when the cholinergic projections to the cortex or hippocampus are severed [52]. However, chronic blockade of $\alpha 4 \beta 2$ receptors in the mediodorsal thalamic nucleus with local infusion of DH E improves memory, an effect reversed by chronic systemic nicotine [62]. Chronic infusion of the $\alpha 4 \beta 2$ antagonist DH E into the ventral hippocampus impairs working memory, an effect which is reversed by acute systemic (SC) nicotine injections [62]. However, more global lesions of the hippocampal target areas of the septohippocampal projection blocks systemic nicotine induced memory improvement [78].

The relationship between acute and chronic nicotinic actions to improve cognition are still not clear. A variety of studies have demonstrated the improvement in cognitive function with acute doses of nicotine [1]. This has been seen with attention, learning and memory. It has also been found that chronic infusions of nicotine via osmotic minipumps and similar methods also improves cognitive function. The similarities and differences in mechanisms of effect with the procognitive effects of acute and chronic nicotine need to be the topic of further investigation.

5. Conclusions

A variety of novel ligands for nicotinic receptors are being developed for treatment of cognitive impairment such as is seen with Alzheimer's disease, attention deficit hyperactivity disorder (ADHD) and the cognitive impairment of schizophrenia. To facilitate the development of nicotinic therapeutics for cognitive function it is necessary to have a better knowledge of the role of receptor activation vs. desensitization and the circuit basis of how nicotinic receptors interact with related neural systems in the basis of cognitive function. Further research will build on our previous research to determine the degree to which nicotine-induced improvements in memory and attention depend on agonist vs. net antagonist effects by desensitization and how nicotinic receptor systems interact with the broader neural circuits underlying these cognitive functions with studies of the actions of nicotinic receptors in particular brain areas. This will lay a firmer foundation for the clinical development of nicotinic treatments for cognitive disorders.

Classically, stimulation of nicotinic receptors was considered to be the key action for nicotine-induced cognitive improvement. However, given that nicotinic receptors are easily desensitized and nicotinic agonists are also desensitizing agents, the relative roles of nicotinic receptor activation vs. desensitization and net antagonist actions has not been well worked out. The foundation that nicotinic antagonist effects can improve cognitive function is supported by studies in our lab and others'. We have found a particular locale in the dorsomedial thalamic nucleus that appears to be key for this effect. If we can more fully determine the relative importance of nicotinic activation vs. deactivation for cognitive improvement and how that plays out in chronic treatment, we can aid the optimal development of nicotinic therapeutics. Nicotinic receptor systems interact with other neural systems in the circuits underlying cognitive function. In neurodegenerative conditions such as Alzheimer's disease where specific patterns of neuronal and receptor loss develop, the

understanding of therapeutic effects with anatomically defined receptor blockade can be informative for therapeutic response. The currently underappreciated that net antagonist effects of nicotine (via receptor desensitization) play important in cognitive improvement and that net decreases in nicotinic receptor activation could provide therapeutic benefit.

Nicotine and other nicotinic agonists have been found to cause improvement in cognitive function, including improved attention and memory. However, since nicotinic receptors are easily desensitized, it is not clear to what degree this improvement is due to the agonist effect of these drugs and how much to the receptor desensitization and net antagonist effects.

References

1. Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: Behavioral characterization, pharmacological specification and anatomic localization. *Psychopharmacology*. 2006; 184:523–39. [PubMed: 16220335]
2. Levin ED, Rezvani AH. Development of nicotinic drug therapy for cognitive disorders. *Eur J Pharmacol*. 2000; 393:141–6. [PubMed: 10771007]
3. Newhouse PA, Potter A, Levin ED. Nicotinic system involvement in Alzheimer's and Parkinson's diseases: Implications for therapeutics. *Drug Aging*. 1997; 11:206–28.
4. Rezvani AH, Levin ED. Cognitive effects of nicotine. *Biol Psychiat*. 2001; 49:258–67. [PubMed: 11230877]
5. Ochoa ELM, Chattopadhyay A, McNamee MG. Desensitization of the nicotinic acetylcholine receptor: Molecular mechanisms and effect of modulators. *Cell Mol Neurobiol*. 1989; 9:141–78. [PubMed: 2663167]
6. Paradiso KG, Steinbach JH. Nicotine is highly effective at producing desensitization of rat alpha4beta2 neuronal nicotinic receptors. *J Physiol*. 2003; 553:857–71. [PubMed: 14555718]
7. Buccafusco JJ, Brach JW, Terry AV. Desensitization of nicotinic acetylcholine receptors as a strategy for drug development. *J Pharmacol Exp Ther*. 2009; 328:364–70.
8. Picciotto MR, Addy NA, Mineur YS, Brunzell DH. It is not "either/or": activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors related to nicotine addiction and mood. *Prog Neurobiol*. 2008; 84:329–42. [PubMed: 18242816]
9. Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology*. 2010; 210:453–69. [PubMed: 20414766]
10. Newhouse PA, Potter A, Singh A. Effects of nicotinic stimulation on cognitive performance. *Curr Opin Pharmacol*. 2004; 4:36–46. [PubMed: 15018837]
11. Levin, ED.; Simon, BB.; Conners, CK. Nicotine effects and attention deficit disorder. In: Newhouse, P.; Piasecki, M., editors. *Nicotine in Psychiatry: Psychopathology and Emerging Therapeutics*. New York: John Wiley; 2000. p. 203–14.
12. Mancuso G, Warburton DM, Melen M, Sherwood N, Tirelli E. Selective effects of nicotine on attentional processes. *Psychopharmacology*. 1999; 146:199–204. [PubMed: 10525756]
13. Lawrence NS, Ross TJ, Stein EA. Cognitive mechanisms of nicotine on visual attention. *Neuron*. 2002; 36:539–48. [PubMed: 12408855]
14. Kumari V, Gray JA, Ffych DH, Mitterschiffthalar MT, Das M, Zachariah E, et al. Cognitive effects of nicotine in humans: An fMRI study. *NeuroImage*. 2003; 19:1002–13. [PubMed: 12880828]
15. Levin ED, Rezvani AH. Nicotinic treatment for cognitive dysfunction. *Curr Drug Target CNS Neurol Disord*. 2002; 1:423–31.
16. Newhouse P, Singh A, Potter A. Nicotine and nicotinic receptor involvement in neuropsychiatric disorders. *Curr Top Med Chem*. 2004; 4:267–82. [PubMed: 14754447]
17. Newhouse PA, Kellar K, Aisen P, White H, Wesnes K, Coderre E, et al. Transdermal nicotine treatment of mild cognitive impairment: a six-month double-blind pilot clinical trial. *Neurology*. 2012; 78:91–101. [PubMed: 22232050]
18. Court J, Martin-Ruiz C, Piggott M, Sperden D, Griffiths M, Perry E. Nicotinic receptor abnormalities in Alzheimer's disease. *Biol Psychiatry*. 2001; 49:175–84. [PubMed: 11230868]

19. Kendziorra K, Meyer P, Wolf H, Barthel H, Hesse S, Seese A, et al. Cerebral nicotinic acetylcholine receptors (nAChRs) in patients with Alzheimer's disease (AD) assessed with 2-F18-A85380 (2-FA) PET – Correlations to dementia severity. *J Nucl Med*. 2006; 47 (Supplement 1): 8P.
20. Nordberg A. Nicotinic receptor abnormalities of Alzheimer's disease: therapeutic implications. *Biol Psychiat*. 2001; 49:200–10. [PubMed: 11230871]
21. White HK, Levin ED. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. *Psychopharmacology*. 1999; 143:158–65. [PubMed: 10326778]
22. Hilt D, Gawryl M, Koenig G. Safety, tolerability and cognitive effects of a novel $\alpha 7$ nicotinic receptor agonist in Alzheimer's disease patients on stable donepezil or rivastigmine therapy. *Alzheimer's & Dementia*. 2009; 5:e32.
23. Meltzer HY, Thompson PA, Lee MA, Ranjan R. Neuropsychologic deficits in schizophrenia: relation to social function and effect of antipsychotic drug treatment. *Neuropsychopharmacology*. 1996; 14:27S–33S. [PubMed: 8866741]
24. Alam DA, Janicak PG. The role of psychopharmacotherapy in improving the long-term outcome of schizophrenia. *Essential Psychopharmacol*. 2005; 6:127–40.
25. Court JA, Piggott MA, Lloyd S, Cookson N, Ballard CG, McKeith IG, et al. Nicotine binding in human striatum: elevation in schizophrenia and reductions in dementia with Lewy bodies, Parkinson's disease and Alzheimer's disease and in relation to neuroleptic medication. *Neuroscience*. 2000; 98:79–87. [PubMed: 10858614]
26. Lee MA, Jayathilake K, Meltzer HY. A comparison of the effect of clozapine with typical neuroleptics on cognitive function in neuroleptic-responsive schizophrenia. *Schizophr Res*. 1999; 37:1–11. [PubMed: 10227103]
27. Mortimer AM. Cognitive function in schizophrenia--do neuroleptics make a difference? *Pharmacol Biochem Behav*. 1997; 56:789–95. [PubMed: 9130306]
28. Green MF. Stimulating the development of drug treatments to improve cognition in schizophrenia. *Ann Rev Clin Psychol*. 2007; 3:159–80. [PubMed: 17716052]
29. Geyer MA, Tamminga CA. Measurement and treatment research to improve cognition in schizophrenia: neuropharmacological aspects. *Psychopharmacology*. 2004; 174:1–2.
30. Martin LF, Kem WR, Freedman R. Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. *Psychopharmacology*. 2004; 174:54–64. [PubMed: 15205879]
31. Terry AV. Role of the central cholinergic system in the therapeutics of schizophrenia. *Curr Neuropharmacol*. 2008; 6:97–101. [PubMed: 19305790]
32. Levin ED, Conners CK, Sparrow E, Hinton SC, Erhardt D, Meck WH, et al. Nicotine effects on adults with attention-deficit/hyperactivity disorder. 1996; 123:55–63.
33. Levin ED, Conners CK, Silva D, Canu W, March J. Effects of chronic nicotine and methylphenidate in adults with attention deficit/hyperactivity disorder. *Exp Clin Psychopharmacol*. 2001; 9:83–90. [PubMed: 11519638]
34. Potter AS, Newhouse PA. Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. 2003; 176:182–94.
35. Wilens TE, Biederman J, Spencer TJ, Bostic J, Prince J, Monuteaux MC, et al. A pilot controlled clinical trial of ABT-418, a cholinergic agonist, in the treatment of adults with attention deficit hyperactivity disorder. *Amer J Psychiat*. 1999; 156:1931–7. [PubMed: 10588407]
36. Potter AS, Ryan K, Newhouse PA. Effects of acute ultra-low dose mecamylamine on cognition in adult attention-deficit/hyperactivity disorder (ADHD). *Human Psychopharmacol Clin Exp*. 2009; 24:309–17.
37. Levin ED. Chronic haloperidol administration does not block acute nicotine-induced improvements in radial-arm maze performance in the rat. *Pharmacol Biochem Behav*. 1997; 58:899–902. [PubMed: 9408193]
38. Felix R, Levin ED. Nicotinic antagonist administration into the ventral hippocampus and spatial working memory in rats. *Neuroscience*. 1997; 81:1009–17. [PubMed: 9330363]
39. Levin ED, Christopher NC. Persistence of nicotinic agonist RJR 2403 induced working memory improvement in rats. *Drug Develop Res*. 2002; 55:97–103.

40. Kruk-Slomka M, Budzynska B, Biala G. Involvement of cholinergic receptors in the different stages of memory measured in the modified elevated plus maze test in mice. *Pharmacological Reports*. 2012; 64:1066–80. [PubMed: 23238464]
41. Mirza NR, Bright JL. Nicotine-induced enhancements in the five-choice serial reaction time task in rats are strain-dependent. *Psychopharmacology*. 2001; 154:8–12. [PubMed: 11292010]
42. Rezvani AH, Levin ED. Nicotinic-glutamatergic interactions and attentional performance on an operant visual signal detection task in female rats. *Eur J Pharmacol*. 2003; 465:83–90. [PubMed: 12650836]
43. Rezvani AH, Kholdebarin E, Dawson E, Levin ED. Nicotine and clozapine effects on attentional performance impaired by the NMDA antagonist dizocilpine in female rats. *Int J Neuropsychopharmacol*. 2008; 11:63–70.
44. Stoleran IP, Mirza NR, Hahn B, Shoaib M. Nicotine in an animal model of attention. *Eur J Pharmacol*. 2000; 393:147–54. [PubMed: 10771008]
45. Rezvani AH, Levin ED. Nicotine-alcohol interactions and attentional performance on an operant visual signal detection task in female rats. *Pharmacol Biochem Behav*. 2003; 76:75–83. [PubMed: 13679219]
46. Rezvani AH, Bushnell PJ, Levin ED. Nicotine and mecamylamine effects on choice accuracy in an operant signal detection task. *Psychopharmacology*. 2002; 164:369–75. [PubMed: 12457266]
47. Grottick AJ, Higgins GA. Effect of subtype selective nicotinic compounds on attention as assessed by the five-choice serial reaction time task. *Behav Brain Res*. 2000; 117:197–208. [PubMed: 11099773]
48. Ruotsalainen S, Miettinen R, MacDonald E, Koivisto E, Sirvio J. Blockade of muscarinic, rather than nicotinic, receptors impairs attention, but does not interact with serotonin depletion. *Psychopharmacology*. 2000; 148:111–23. [PubMed: 10663425]
49. McGaughy J, Decker MW, Sarter M. Enhancement of sustained attention performance by the nicotinic acetylcholine receptor agonist ABT-418 in intact but not basal forebrain-lesioned rats. *Psychopharmacology*. 1999; 144:175–82. [PubMed: 10394999]
50. Terry AVJ, Risbrough VB, Buccafusco JJ, Menzaghi F. Effects of (+/-)-4-[[2-(1-methyl-2-pyrrolidinyl)ethyl]thio]phenol hydrochloride (SIB-1553A), a selective ligand for nicotinic acetylcholine receptors, in tests of visual attention and distractibility in rats and monkeys. *J Pharmacol Exp Ther*. 2002; 301:284–92. [PubMed: 11907185]
51. Mirza NR, Stoleran IP. Nicotine enhances sustained attention in the rat under specific task conditions. *Psychopharmacology*. 1998; 138:266–74. [PubMed: 9725748]
52. Levin ED, Christopher NC, Briggs SJ, Rose JE. Chronic nicotine reverses working memory deficits caused by lesions of the fimbria or medial basalocortical projection. *Cog Brain Res*. 1993; 1:137–43.
53. Rezvani AH, Levin ED. Nicotine-antipsychotic drug interactions and attentional performance in female rats. *Eur J Pharmacol*. 2004; 486:175–82. [PubMed: 14975706]
54. Rezvani AH, Cauley M, Sexton H, Xiao X, Brown ML, Paige MA, et al. Sazetidine-A, a selective 4/2 nicotinic acetylcholine receptor desensitizing agent reverses dizocilpine and scopolamine-induced attentional impairments in rats. *Psychopharmacology*. 2011; 215:621–30. [PubMed: 21274704]
55. Levin ED, Cauley M, Rezvani AH. Improvement of attentional function with antagonism of nicotinic receptors in female rats. *Eur J Pharmacol*. 2013; 702:269–74. [PubMed: 23399762]
56. Rezvani AH, Kholdebarin E, Brucato FH, Callahan PM, Lowe DA, Levin ED. Effect of R3487/MEM3454, a novel nicotinic $\alpha 7$ receptor partial agonist and 5-HT₃ antagonist on sustained attention in rats. *Prog Neuropsychopharmacol Biol Psychiat*. 2009; 33:269–75.
57. Levin ED, Caldwell DP. Low-dose mecamylamine improves learning of rats in the radial-arm maze repeated acquisition procedure. *Neurobiol Learn Mem*. 2006; 86:117–22. [PubMed: 16632386]
58. Levin ED, Bettgowda C, Blosser J, Gordon J. AR-R17779, an $\alpha 7$ nicotinic agonist, improves learning and memory in rats. *Behav Pharmacol*. 1999; 10:675–80. [PubMed: 10780509]
59. Levin ED, Christopher NC. Lobeline-induced learning improvements in rats in the radial-arm maze. *Pharmacol Biochem Behav*. 2003; 76:133–9. [PubMed: 13679226]

60. Bancroft A, Levin ED. Ventral hippocampal $\alpha 4 \beta 2$ nicotinic receptors and chronic nicotine effects on memory. *Neuropharmacology*. 2000; 39:2770–8. [PubMed: 11044746]
61. Bettany JH, Levin ED. Ventral hippocampal $\alpha 7$ nicotinic receptor blockade and chronic nicotine effects on memory performance in the radial-arm maze. *Pharmacol Biochem Behav*. 2001; 70:467–74. [PubMed: 11796146]
62. Arthur D, Levin ED. Chronic inhibition of $\alpha 4 \beta 2$ nicotinic receptors in the ventral hippocampus of rats: Impacts on memory and nicotine response. *Psychopharmacology*. 2002; 160:140–5. [PubMed: 11875631]
63. Levin ED, Bradley A, Addy N, Sigurani N. Hippocampal $\alpha 7$ and $\alpha 4 \beta 2$ nicotinic receptors and working memory. *Neuroscience*. 2002; 109:757–65. [PubMed: 11927157]
64. Nott A, Levin ED. Dorsal hippocampal $\alpha 7$ and $\alpha 4 \beta 2$ nicotinic receptors and memory. *Brain Res*. 2006; 1081:72–8. [PubMed: 16556437]
65. Pocivavsek A, Icenogle L, Levin ED. Hippocampal $\alpha 7$ and $\alpha 4 \beta 2$ nicotinic receptors and clozapine effects on memory. *Psychopharmacology*. 2006; 188:596–604.
66. Addy NA, Nakijama A, Levin ED. Nicotinic mechanisms of memory: effects of acute local DH E and MLA infusions in the basolateral amygdala. *Cog Brain Res*. 2003; 16:51–7.
67. Clarke PB, Schwartz RD, Paul SM, Pert CB, Pert A. Nicotinic binding in rat brain: autoradiographic comparison of [3 H]acetylcholine, [3 H]nicotine, and [125 I]- α -bungarotoxin. *J Neurosci*. 1985; 5:1307–15. [PubMed: 3998824]
68. Sanders D, Simkiss D, Braddy D, Baccus S, Morton T, Cannady R, et al. Nicotinic receptors in the habenula: Importance for memory. *Neuroscience*. 2010; 166:386–90. [PubMed: 20034548]
69. Cannady R, Weir R, Wee B, Gotschlich E, Kolia N, Lau E, et al. Nicotinic antagonist effects in the mediodorsal thalamic nucleus: regional heterogeneity of nicotinic receptor involvement in cognitive function. *Biochem Pharmacol*. 2009; 78:788–94. [PubMed: 19477167]
70. Levin ED, Perkins A, Brotherton T, Qazi M, Berez C, Montalvo-Ortiz J, et al. Chronic underactivity of medial frontal cortical $\alpha 2$ -containing nicotinic receptors increases clozapine-induced working memory impairment in female rats. *Prog Neuro-Psychopharmacol Biol Psychiat*. 2009; 33:296–302.
71. Levin ED, Briggs SJ, Christopher NC, Auman JT. Working memory performance and cholinergic effects in the ventral tegmental area and substantia nigra. *Brain Res*. 1994; 657:165–70. [PubMed: 7820615]
72. Kim JS, Levin ED. Nicotinic, muscarinic and dopaminergic actions in the ventral hippocampus and the nucleus accumbens: effects on spatial working memory in rats. *Brain Res*. 1996; 725:231–40. [PubMed: 8836529]
73. Thomsen MS, Christensen DZ, Hansen HH, Redrobe JP, Mikkelsen JD. $\alpha 7$ Nicotinic acetylcholine receptor activation prevents behavioral and molecular changes induced by repeated phencyclidine treatment. *Neuropharmacology*. 2009; 56:1001–9. [PubMed: 19233218]
74. Rezvani AH, Cauley M, Xiao Y, Kellar KJ, Levin ED. Effects of chronic sazetidine-A, a selective $\alpha 2^*$ nicotinic receptor desensitizing agent on pharmacologically-induced impaired sustained attention in rats. *Psychopharmacology*. 2012; 222:269–76. [PubMed: 22297831]
75. Zwart R, Carbone AL, Moroni M, Bermudez I, Mogg AJ, Folly EA, et al. Sazetidine-A is a potent and selective agonist at native and recombinant $\alpha 4 \beta 2$ nicotinic acetylcholine receptors. *Mol Pharmacol*. 2008; 73:1838–43. [PubMed: 18367540]
76. Levin ED, Briggs SJ, Christopher NC, Rose JE. Chronic nicotinic stimulation and blockade effects on working memory. *Behav Pharmacol*. 1993; 4:179–82. [PubMed: 11224184]
77. Levin ED, Kim P, Meray R. Chronic nicotine working and reference memory effects in the 16-arm radial maze: interactions with D1 agonist and antagonist drugs. *Psychopharmacology (Berl)*. 1996; 127:25–30. [PubMed: 8880940]
78. Levin ED, Christopher NC, Weaver T, Moore J, Brucato F. Ventral hippocampal ibotenic acid lesions block chronic nicotine-induced spatial working memory improvement in rats. *Cognitive Brain Research*. 1999; 7:405–10. [PubMed: 9838204]

Figure 1.

Acute nicotine treatment reverses the attentional impairment caused by acute administration of the NMDA glutamate antagonist dizocilpine (MK-801) seen in hit percent correct (mean ±sem) in visual signal detection task. Data from [43].

Sazetidine-A Reversal of Dizocilpine Induced Attentional Impairment: Signal Detection Task

Figure 2.

Acute administration of the $\alpha 2$ nicotinic desensitizing agent sazetidine-A reverses the attentional impairment caused by acute administration of the NMDA glutamate antagonist dizocilpine seen with hit percent correct (mean $\pm$ sem) in visual signal detection task. Data from [54].

Nicotine Interactions with the DH β E Therapeutic Effect

Figure 3.

Acute DH β E (a competitive α 2 nicotinic receptor antagonist) reverses the attentional impairment caused by acute administration of the NMDA glutamate antagonist dizocilpine seen with hit percent correct (mean $\pm$ sem) in visual signal detection task [55].

Nicotine Interactions with the MLA Therapeutic Effect

Figure 4.

Acute MLA (a competitive $\alpha 7$ nicotinic receptor antagonist) reverses the attentional impairment caused by acute administration of the NMDA glutamate antagonist dizocilpine seen with hit percent correct (mean $\pm$ sem) in visual signal detection task [55].