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Development of nicotinic drug therapy for cognitive disorders

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Abstract

Nicotine, as well as other nicotinic drugs, may provide useful therapeutic treatment for a variety of cognitive impairments including those found in Alzheimer's disease, schizophrenia and attention deficit hyperactivity disorder (ADHD). We have found that nicotine skin patches significantly improve attentional performance in people with these disease states as well as normal nonsmoking adults. Animal models are critical for determining the neurobehavioral bases for nicotinic effects on cognitive function. We have found in lesion and local infusion studies with rats that the hippocampus is an important substrate for nicotinic effects on working memory function. Both $\alpha 7$ and $\alpha 4\beta 2$ nicotinic receptors in the hippocampus are involved. Further work has investigated the relationship of nicotinic systems with dopaminergic and glutaminergic systems in the basis of cognitive function. Nicotine has proven to be a useful prototypic compound for the family of nicotinic compounds. It produces cognitive improvements in both animal models and clinical populations. Recent work with more selective nicotinic receptor agonists and antagonists in animal models is providing important information concerning the neural mechanisms for nicotinic involvement in cognitive function and opening avenues for development of safe and effective nicotinic treatments for clinical use.

Keywords: Nicotine; Attention; Learning; Memory

1. Introduction

Nicotine, the primary psychoactive ingredient in tobacco, has been found in a variety of studies with experimental animals (Levin and Simon, 1998) and humans (Newhouse et al., 1997) to improve cognitive performance. Nicotine itself delivered via means other than tobacco, such as nicotine patches may prove to be an effective treatment for cognitive impairment such as is seen in Alzheimer's disease, schizophrenia and attention deficit hyperactivity disorder (ADHD) in adults. Novel nicotinic receptor ligands currently under development have also shown evidence for providing cognitive improvement (Brioni et al., 1997). These nicotinic analogs may provide the beneficial effects of nicotine with fewer adverse side effects by selectively interacting with nicotinic receptor subtypes involved with cognitive function, but not with nicotinic receptor subtypes involved with adverse effects such as those involved with the cardiovascular system or reinforcement.

It is crucial in the development of nicotinic therapy for cognitive impairment to understand the basic involvement of nicotinic systems with cognitive function, so that the important receptor subtypes can be targeted. Animal models are essential in the development of novel nicotinic treatments for cognitive impairment. Not only can they serve to test the functional effects of new nicotinic ligands; they can also help determine the critical mechanisms for nicotinic induced cognitive improvement.

2. Clinical studies of nicotine effects on attention

In clinical studies, nicotine-induced cognitive improvement has been most clearly seen in tests of attention. We have found in a series of studies that nicotine skin patch administration improves performance on the Connors continuous performance task (CPT), a computerized test of attention.

The Conners CPT is a valid assessment tool for diagnosing ADHD and is sensitive to stimulant therapy (Con-

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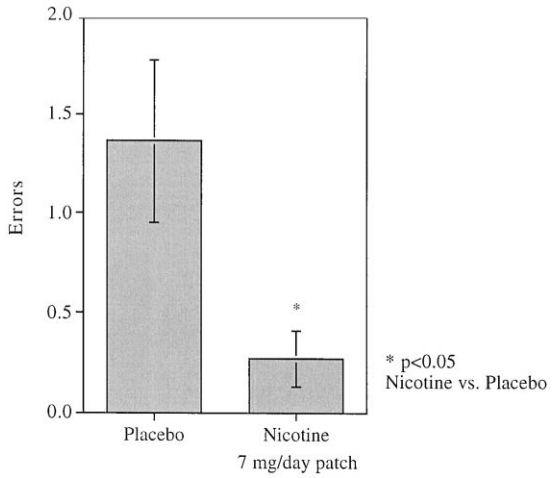

Fig. 1. Nicotine skin patch effects on CPT Normal nonsmoking adults.

ners, 1994, 1995). It is a 14-min test in which the subject is instructed to respond as quickly as possible to a target stimulus, but to refrain from responding to a more rarely occurring nontarget stimulus. In this way the Conners CPT differs from other CPTs in which the subject is to respond to rarely occurring stimuli. This difference makes the Conners CPT sensitive to problems individuals may have in withholding inappropriate responses. Dependent measures include errors of omission and commission, hit reaction time (reaction time for correct responses) and the variability in hit reaction time measured over trial blocks during the course of the session and over different interstimulus intervals (ISI) of 1, 2 and 4 s. On the Conners CPT, response time variability typically increases over the course of the session and with longer ISIs. The hypothesis was that the drug treatments would decrease this degradation of performance.

2.1. Normal adult nonsmokers

An important baseline effect of nicotine on attention is its effect in normal, nonsmoking adults. Withdrawal from nicotine in deprived smokers has been shown to cause attentional impairments (Hatsukami et al., 1989) which may cloud the interpretation of the effects of nicotine effects on attention. However, Warburton has demonstrated improvements with nicotine administration even in the absence of withdrawal effects (Warburton and Arnall, 1994) and with the nicotine skin patch (Warburton and Mancuso, 1998). Still, the best way to determine the effects of nicotine without the potential effect of smoking withdrawal is to conduct studies in nonsmokers. Also, given that they do not show baseline cognitive impairment, they provide an important group for understanding nicotine effects on normal cognitive performance relative to effects in reversing impaired performance as discussed below. As shown in Fig. 1, we have found that low dose nicotine skin patches (7 mg/day) significantly reduced errors of omission on the CPT task in normal nonsmoking adults (Levin et al., 1998a). Importantly, there was not a nicotine-induced increase in errors of commission. In fact, these errors showed a slight though nonsignificant decrease in commission error rates from 9.8 ± 2.0 with placebo to 7.6 ± 1.1 with nicotine. This provides evidence that the nicotine-induced decrease in errors of omission was not merely due to a shift in response strategy to increased response rate. In this study, no changes were seen in hit reaction time or reaction time variability.

2.2. Alzheimer's disease patients

Alzheimer's disease has been shown in a variety of studies to be accompanied by a dramatic reduction in nicotinic receptors in the cortex and hippocampus (Quiron et al., 1986; Shimohama et al., 1986; Perry et al., 1987; Giacobini et al., 1988; Nordberg et al., 1988; Kellar and Wonnacott, 1990; Sugaya et al., 1990; Rinne et al., 1991; Schroder et al., 1995). Several different groups have found that nicotine injections or nicotine skin patches significantly improve attention (Sahakian and Jones, 1991; Jones et al., 1992; White and Levin, 1999), memory (Newhouse et al., 1988; Parks et al., 1996) and learning (Wilson et al., 1995) in Alzheimer's disease patients (for review see Newhouse et al., 1997). We have conducted a series of studies to determine nicotine skin patch effects on attentiveness in Alzheimer's patients. As in the studies with normal adult subjects we used the Connors CPT. The CPT performance of Alzheimer's disease patients is considerably impaired relative to normal adults as can be seen by the omission error rates shown in the placebo condition (Fig. 2). However, similar to normal adults, we have found that nicotine skin patches significantly reduce errors of omission on the CPT task in nonsmoking patients with Alzheimer's disease (White and Levin, 1999). As with the normal nonsmoking adults there was not a nicotine effect on errors of commission. This provides evidence that the nicotine-induced decrease in omission errors was not merely due to a shift to more frequent responding. Nicotine treatment also significantly decreased variability of hit

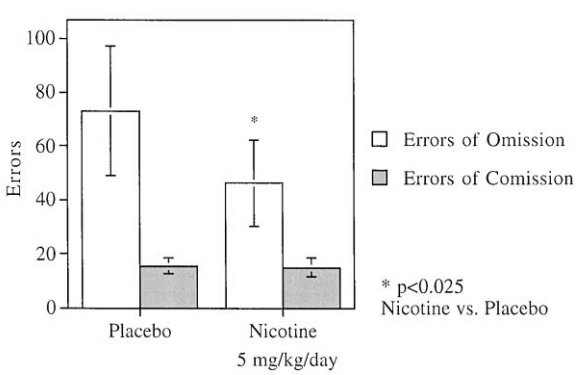

Fig. 2. Nicotine skin patch effects on CPT Alzheimer's disease patients.

response time. Importantly, the beneficial effect in the Alzheimer's disease patients persisted for the 4 weeks of nicotine administration. This is similar to the persistence of effect we have seen in our chronic studies with rats (see below). In an earlier study, Wilson et al. (1995) found the positive effect of nicotine skin patch administration to persist for at least 8 days of continued administration. Persistence of effectiveness of treatment is a necessary aspect for treatment of a chronic disorder like Alzheimer's disease.

2.3. Schizophrenics

The great majority (about 80%) of schizophrenics are regular smokers (Hughes et al., 1986). One possibility is that they self-medicate to attenuate problems resulting from schizophrenia and/or to attenuate problems resulting from antipsychotic medication. Schizophrenics appear to have a deficient number of nicotinic receptors, especially in the hippocampus (Freedman et al., 1995; Leonard et al., 1996). Adler et al. (1993) have found that cigarette smoking normalized the sensory gating deficits seen in schizophrenics. In adult schizophrenics who were smokers (Levin et al., 1996b), we found evidence for both sorts of self-medication. In a study within a project to determine the efficacy of different doses of the antipsychotic haloperidol, we examined the cognitive effects of 0, 7, 14 and 21 mg/day nicotine skin patches. In terms of CPT response speed variability, nicotine caused a dose-related reduction in all haloperidol dose groups (Fig. 3). In terms of a delayed matching to sample working memory test, we found significant nicotine induced reversal of haloperidol-induced deficits. No nicotine effects were seen in the low dose haloperidol group (Fig. 4). In schizophrenic patients, there is evidence that nicotine has effect in both reversing the adverse effects of antipsychotic drugs and the cognitive impairment of schizophrenia itself.

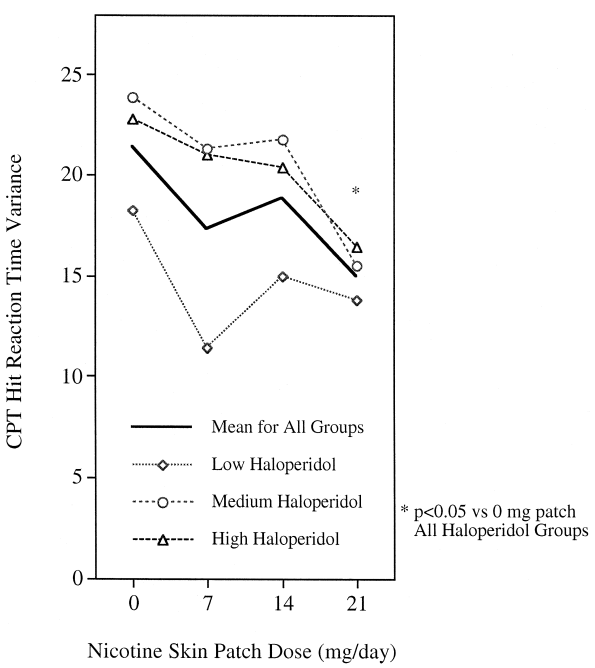

Fig. 3. Nicotine skin patch effects on CPT in schizophrenic patients.

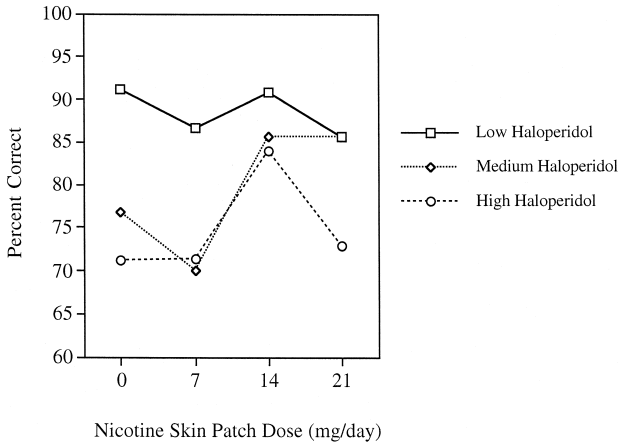

Fig. 4. Nicotine skin patch effects on delayed matching to sample in schizophrenics.

2.4. Adults with ADHD

In adults with ADHD (Conners et al., 1996; Levin et al., 1996c), we have shown that nicotine skin patch treatment significantly ($p < 0.005$) reduced clinical ADHD symptoms as measured by the standardized Clinical Global Impressions Scale (Fig. 5). In the CPT, nicotine treatment reduced variability of response speed over the different blocks of the test session, an indication of improvement in attentional consistency. However, nicotine did not cause a significant reduction in CPT errors as it did in normal adults and patients with Alzheimer's disease. Recently, Biederman et al. (Wilens et al., 1999) have found that the

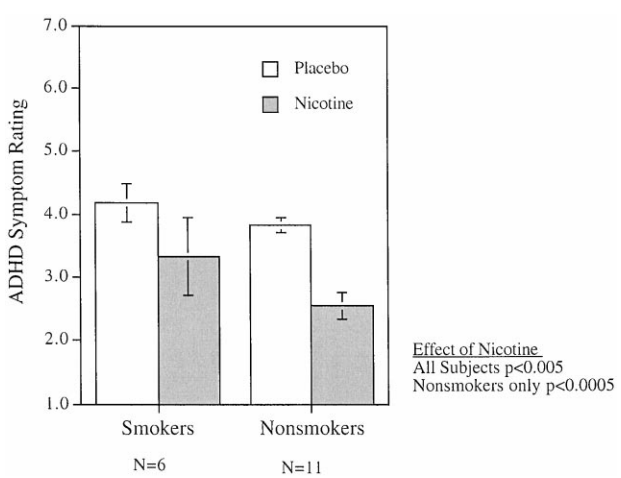

Fig. 5. Nicotine skin patch effects on adults with ADHD.

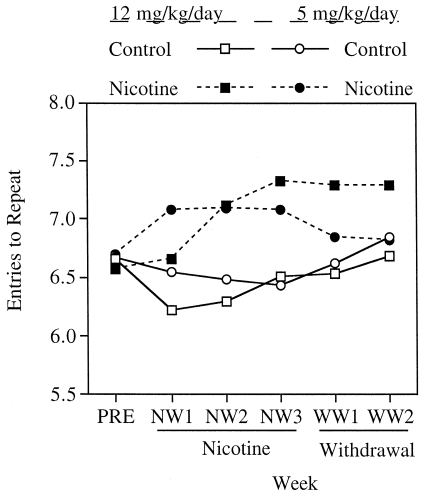

Fig. 6. Chronic nicotine effects on rats on radial-arm maze choice accuracy.

nicotinic agonist ABT-418 is also effective in reducing symptoms of inattention in adults with ADHD.

3. Cognitive effects of nicotine in animal models

In rat (for reviews see Brioni et al., 1997; Levin and Simon, 1998) and monkey (Elrod et al., 1988; Jackson and Buccafusco, 1989) models nicotine-induced cognitive improvement is more clearly seen in terms of effects on memory performance. These models are important for the determination of the mechanisms of nicotinic induced cognitive improvement.

In a series of studies with rats, we have found that acute treatment with nicotine (Levin and Rose, 1991) and other nicotinic receptor agonists such as dimethylenthanolamine (Levin et al., 1995), epibatidine (Levin et al., 1996d), isonicotine, norisonicotine (Levin et al., 1999d), and AR-R 17779 (Levin et al., 1999a) significantly improve memory performance in the eight-arm radial maze. Importantly, for possible clinical use we have found that the efficacy of nicotine improvement of memory does not diminish with chronic administration. As shown in Fig. 6, we have found that chronic infusion of either 5 or 12 mg/kg/day of nicotine significantly improves memory performance on the eight-arm maze over 3–4 weeks of treatment (Levin and Rose, 1990; Levin et al., 1990a, 1993a). The improvement caused by the higher dose persists for several weeks after withdrawal (Levin et al., 1992), while performance with the lower dose returns to control levels after withdrawal (Levin et al., 1993a). In contrast, the nicotinic antagonist mecamylamine impairs radial-arm maze choice accuracy (Levin et al., 1987, 1990b) and chronic co-administration of mecamylamine with chronic nicotine infusion blocks the nicotine-induced memory improvement (Levin et al., 1993a).

Nicotine-induced radial-arm maze memory improvement is specific to working memory with no apparent effect on reference memory. When rats are tested in the larger 16-arm maze, both working and reference memory can be easily measured simultaneously. We have found that both acute (Levin et al., 1997) and chronic (Levin et al., 1996a) nicotine treatment specifically improved working memory performance.

We have found the hippocampus to be important for chronic nicotinic involvement in memory function. Small hippocampal ibotenic acid lesions, which did not significantly impair working memory performance, block the chronic nicotine-induced memory improvement (Levin et al., 1999c). The critical site of action for chronic nicotine in the hippocampus appears to be postsynaptic to the septohippocampal projection since chronic nicotine-induced memory improvement was not attenuated by knife-cut lesions of this fiber bundle (Levin et al., 1993b). Both $\alpha 4\beta 2$ and $\alpha 7$ nicotinic receptor subtypes in the hippocampus are important for working memory function. As shown in Fig. 7, memory in the radial-arm maze was impaired by local hippocampal infusion of either DHβE, the $\alpha 4\beta 2$

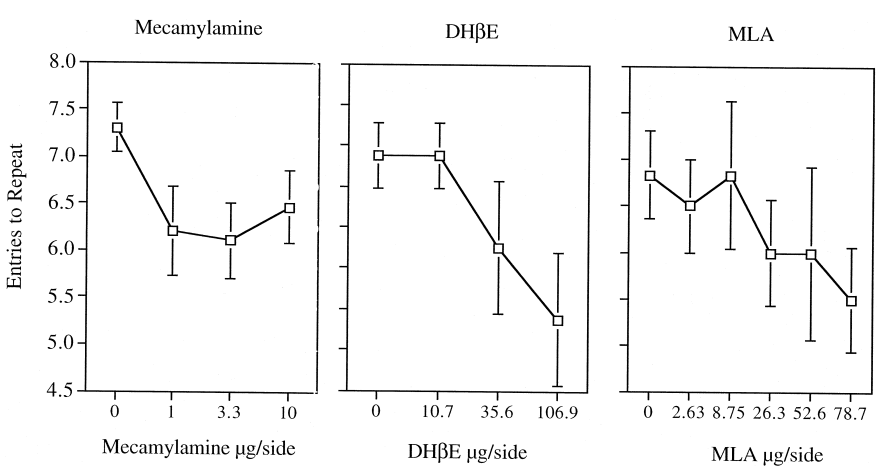

Fig. 7. Acute nicotinic antagonist infusion into the ventral hippocampus and radial-arm maze choice accuracy.

receptor antagonist, or MLA, the α7 receptor antagonist (Felix and Levin, 1997; Levin et al., 1999b) as well as the nicotinic channel blocker mecamylamine (Kim and Levin, 1996).

The working memory impairment caused by the nicotinic antagonist mecamylamine was reversed by the dopamine D_2 receptor agonist quinpirole (Levin et al., 1989) and potentiated by the dopamine D_2 receptor antagonist raclopride (McGurk et al., 1989), but was not affected by dopamine D_1 receptor ligands. These data suggest that nicotine may exert its effect on working memory partly by interacting with dopaminergic systems in the brain and partly with dopamine D_2 receptors. The location of the critical dopamine receptors for this effect is still unclear. Dopamine receptors in the nucleus accumbens which are important for the rewarding effects of nicotine do not appear to be important for the memory-enhancing effects of nicotine (Grigoryan et al., 1996). We have also found that infusions of the nicotinic receptor antagonist mecamylamine into the nucleus accumbens do not impair working memory performance in the radial-arm maze (Kim and Levin, 1996). The mecamylamine doses used were the same as were found to be effective when infused into the hippocampus. These results suggest that the reinforcing and memory-enhancing effects of nicotinic action may be separable with novel subtype-specific ligands.

Glutamate systems also appear to interact with nicotinic systems with regard to memory function. Memory deficits caused by the NMDA receptor antagonist dizocilpine were significantly attenuated by nicotine (Levin et al., 1998b).

4. Conclusions

Nicotinic systems play an important role in the neural basis of working memory and attentional function. The development of nicotinic-based therapeutics has an advantage in the availability of the prototypic agonist available for human use in the nicotine skin patch. This enables studies in various clinical populations to determine the proof of principle. For cognitive improvement, this has been performed for Alzheimer's disease, schizophrenia and adults with ADHD. Animal models are important for determining the neurobehavioral mechanisms of the effects. By determining the critical mechanisms of nicotinic effects including critical nicotinic receptor subtypes, their anatomic localization and interactions with other neural systems, we can help both with the understanding of the neurobiology of memory function and the development of therapeutic agents for memory dysfunction.

Acknowledgements

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