

Atomoxetine and nicotine enhance prepulse inhibition of acoustic startle in C57BL/6 mice

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Received 10 September 2004; received in revised form 2 November 2004; accepted 23 November 2004

Abstract

Deficits in sensory-gating, often measured as deficits in prepulse inhibition of acoustic startle (PPI), are associated multiple with disorders including schizophrenia, attention deficit and hyperactivity disorder (ADHD), and withdrawal from nicotine. Drugs that can reverse deficits in PPI may serve as therapeutic agents for nicotine withdrawal, ADHD, and/or schizophrenia. The present study investigated the effects of acute atomoxetine, a norepinephrine reuptake inhibitor, nicotine, and mecamylamine, a nicotinic acetylcholinergic antagonist, on PPI and acoustic startle in C57BL/6 mice. Three doses of atomoxetine (0.2, 2.0, and 20 mg/kg) were administered prior to testing PPI and startle. The 0.2 and 2.0 mg/kg doses enhanced PPI and the 20 mg/kg dose enhanced startle. A second experiment investigated the effects of 2.0 mg/kg atomoxetine and 1.0 mg/kg mecamylamine administered alone or together on PPI and startle. As before, atomoxetine enhanced PPI. Mecamylamine did not alter PPI and did not block the enhancement of PPI by atomoxetine. Neither drug altered startle. A third experiment investigated the effects of 2.0 mg/kg atomoxetine and 0.125 mg/kg nicotine administered alone or together on PPI and startle. Both drugs enhanced PPI when administered alone. However, when co-administered, no enhancement of PPI was seen. Neither nicotine nor atomoxetine altered startle. The present results demonstrate that acute doses of nicotine and atomoxetine enhance PPI independent of effects on startle and that the enhancement of PPI by atomoxetine occurs independent of the nicotinic acetylcholinergic system. Thus, the newly available medication for ADHD, atomoxetine, could be a potential therapeutic agent for disorders associated with disrupted PPI such as withdrawal from nicotine.

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Keywords: Sensory-gating; Norepinephrine; Acetylcholine; Addiction; ADHD; Schizophrenia

In 1988, the US Surgeon General concluded that tobacco products are addictive and that nicotine is the main pharmacological agent in tobacco responsible for its addictive nature [43]. However, nicotine addiction is a complex disorder and the effects of nicotine on neurological/behavioral function are not fully understood. One factor contributing to nicotine dependence is nicotine withdrawal-associated changes in attention and related sensory-gating (i.e., the ability to filter out extraneous information) [21,34]. Nicotine may initially enhance sensory-gating, but withdrawal from chronic nicotine could be accompanied by deficits in sensory-gating. Deficits in sensory-gating, especially as measured by deficits in pre-

pulse inhibition of the acoustic startle response (PPI), are associated with profound psychological deficits [12,26,32,41]. Thus, withdrawal-associated deficits in sensory-gating, as measured with PPI, could contribute to smoking relapse because smokers may attempt to alleviate these sensory-gating deficits by resuming smoking.

Pre-pulse inhibition is thought to measure the ability to filter sensory information or sensory gate, a process important for attention [1,41]. Smoking in non-smokers [9] and acute nicotine administered to rats [2,8] enhanced PPI. However, the nicotinic antagonist mecamylamine at dose of 10 mg/kg decreased PPI in rats [8]. Because mecamylamine can precipitate nicotine withdrawal symptoms in rats [22], withdrawal from nicotine could be associated with deficits in PPI. In fact, nicotine withdrawal after 14 days of chronic nicotine was as-

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sociated with deficits in PPI in DBA/2J mice [39]. Deficits in the ability to sensory gate would suggest stimuli that are normally unobtrusive would become disruptive; this could lead to decrements in cognitive task performance. Indeed, this is believed to be the case for patients with schizophrenia [3,4], and may be the case for withdrawal from nicotine. Thus, drugs that enhance PPI might be potential pharmacological treatments for nicotine withdrawal-associated deficits in sensory-gating.

The noradrenergic system is one potential target for treating nicotine withdrawal-associated deficits in sensory-gating. Noradrenergic processes facilitate learning and may work by increasing attention or gating of sensory information [5,13,23,27,30,40]. Importantly, sensory-gating deficits are seen in patients with attention deficit hyperactivity disorder (ADHD) [6]. The norepinephrine reuptake inhibitor atomoxetine [11] has recently been FDA-approved for the treatment of ADHD [24]. Since noradrenergic antagonism disrupts sensory-gating, as measured by auditory gating [40], theoretically, atomoxetine could enhance PPI, but this has not yet been tested.

It is interesting to note that adolescents with ADHD are twice as likely to become smokers as adolescents that have not been diagnosed with ADHD and acute nicotine administration improved cognitive function in non-smoking adolescents with ADHD [35]. Further, individuals with ADHD show more severe nicotine withdrawal-associated deficits in attention [34]. Since nicotine enhances PPI [2,9] and ADHD is associated with deficits in sensory-gating [6], these findings raise the possibility that individuals with ADHD that smoke may be self-medicating [44].

It is clear that nicotine enhances PPI [2,9]. In the present study we examined if acute atomoxetine and acute nicotine would similarly enhance PPI in C57BL/6 mice. In addition, we tested if the nicotine receptor antagonist mecamylamine would disrupt atomoxetine-mediated effects on PPI.

C57BL/6J mice ($n = 7$ –8 per group; Jackson Laboratories, Bar Harbor, ME) were tested at 2–4 months of age. Mice had ad libitum access to food and water. Mice were maintained on a 12-light:12-h dark cycle (lights on at 07:00 h), and all testing occurred between 09:00 h and 16:00 h. The Temple University Institutional Animal Care and Use Committee approved all behavioral procedures. C57BL/6J mice were chosen for this study based on previous research indicating that this strain reliably demonstrates PPI of acoustic startle [42]. In addition, C57BL/6J have also been used extensively in our laboratory to investigate the effects of nicotine and mecamylamine on learning and behavior [14,17–19,28], which makes this strain appropriate for extending our findings with nicotine to sensory-gating.

Testing occurred in two identical sound attenuating testing chambers (65 cm $\times$ 35 cm $\times$ 25 cm). Each chamber was equipped with a Radio Shack® loudspeaker mounted 25 cm above the holding cylinder. Startle responses were recorded in a commercial startle reflex system (S-R Lab, San Diego Instruments, CA). Mice were placed in a Plexiglas holding

cylinder mounted on a Plexiglas platform. A piezoelectric accelerometer located beneath the platform was used to transform startle responses into units based on force and latency of startle. Data were sampled at 250 samples/s and the maximum voltage attained on each trial was used as the dependent variable.

This protocol is based on a PPI protocol previously described in full detail [15]. Pre-pulse and startle stimuli were white noise. Each session started with a 5 min acclimation period with a 65 dB acoustic background noise followed by five 120 dB startle pulses, in an effort to make subsequent startle trials less variable. Pre-pulse trials followed the initial 120 dB startle acclimation. Each pre-pulse was 20 ms in duration, followed by a 40 ms startle stimulus of 120 dB. There was a 100 ms interstimulus interval between pre-pulse offset and startle stimulus onset. PPI was recorded for pre-pulse intensities of 69, 73, and 81 dB, and no stimulus. Each pre-pulse trial was administered ten times in a random order. Trials of 120 dB alone were randomly interspersed within the pre-pulse trials and used for comparison with the pre-pulse trials. The percent PPI was calculated using the formula $[100 - (\text{response to pre-pulse} + 120 \text{ dB}) / (\text{response for 120 dB alone}) \times 100]$. Acoustic startle trials followed the PPI trials. Startle trials consisted of 40 ms pulses at 0 (no stimulus), 90, 95, 100, 105, 110, 115, and 120 dB. Each trial was presented five times in a randomized order with an intertrial interval randomized from 10 to 20 s. For all trials, data were collected as 60, 1 ms voltage readings.

Experiment One examined the dose dependent effects of atomoxetine on acoustic startle and PPI of acoustic startle. Atomoxetine was administered 30 min prior to a session (0.2, 2.0, or 20.0 mg/kg i.p.). Experiment Two examined the effects of atomoxetine and mecamylamine administered either alone or together on acoustic startle and PPI of acoustic startle. Atomoxetine (2.0 mg/kg i.p.) was administered 30 min prior to behavioral testing and mecamylamine (1.0 mg/kg i.p.) was administered 15 min prior to behavioral testing. The number of injections was equalized across groups. Experiment Three examined the effects of atomoxetine and nicotine administered either alone or together on acoustic startle and PPI of acoustic startle. Atomoxetine (2.0 mg/kg i.p.) was administered 30 min prior to testing and nicotine (0.125 mg/kg i.p.) was administered 5 min before startle testing, dose based on pilot data (not shown) and time of administration based on previous pharmacokinetic studies in mice [33]. The number of injections was equalized across groups.

l-N-Methyl-*g*-(2-methyl-phenoxy) benzenepropanamine hydrochloride (atomoxetine hydrochloride) provided by Eli-Lilly Pharmaceuticals was dissolved in physiological saline (0.9% NaCl) and administered at 0.2, 2.0, or 20.0 mg/kg. Atomoxetine was administered via i.p. injection 30 min prior to behavioral procedures [31]. *N*,2,3,3-Tetramethylbicyclo[2.2.1]heptan-2-amine hydrochloride (mecamylamine hydrochloride; Sigma Chem. Corp., St. Louis, MO) was dissolved in saline and administered at 1.0 mg/kg i.p. (a high dose of mecamylamine that has

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