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Effect of Nicotine, Lobeline, and Mecamylamine on Sensory Gating in the Rat

PETER CURZON,[1] DAVID J. B. KIM AND MICHAEL W. DECKER

Neuroscience Department, Pharmaceutical Products Division, Abbott Laboratories, Building AP-9A (47W), Abbott Park, IL 60064-3500

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CURZON, P., D. J. B. KIM AND M. W. DECKER. *Effect of nicotine, lobeline, and mecamylamine on sensory gating in the rat.* PHARMACOL BIOCHEM BEHAV **49**(4) 877-882, 1994. – In normal subjects, if an acoustic startle stimulus is immediately preceded by a small brief change in background noise intensity, the magnitude of the subsequent startle response is decreased. This prepulse inhibition (PPI) of an acoustic startle response has been shown to be associated with sensorimotor gating. PPI is disrupted in schizophrenic patients and has been linked to attentional disorders characteristic of this disease. We tested the effects of (−)-nicotine, (0.19, 0.62, and 1.9 μmol/kg IP) (equivalent to 0.03, 0.1, and 0.3 mg/kg base) and the nicotinic cholinergic receptor (nAChR) channel blocker, mecamylamine (5.0 and 50 μmol/kg IP) (equivalent to 1.0 and 10.0 mg/kg) on PPI of the acoustic startle response in the rat. Nicotine increased the PPI at the lowest prepulse signal levels but not at the stronger levels. Mecamylamine was without effect at 5.0 μmol/kg, but the 50 μmol/kg dose decreased the inhibition at both weak and strong prepulse (PP) levels. Mecamylamine (5.0 μmol/kg) pretreatment did not block the (−)-nicotine-induced increase in PPI. Lobeline (0.19, 0.62, 1.9, and 6.2 μmol/kg IP) (equivalent to 0.071, 0.23, 0.71, and 2.3 mg/kg) was without effect. These results are consistent with a mecamylamine-insensitive effect of nicotine to improve gating in normal rats. The nAChR subtype involved in producing nicotine's increase of PPI needs further investigation.

Nicotine Lobeline Mecamylamine Acoustic startle Schizophrenia Sensorimotor gating

A STARTLE response to an acoustic stimulus is markedly reduced when that acoustic stimulus is shortly preceded (100 ms) by a less intense acoustic stimulus to which there is no measurable response. This reduction in responsivity has been termed prepulse inhibition (PPI) (27). The use of PPI of the acoustic startle response in the rat has been proposed as a measure of sensorimotor gating (31) as well as a screening test for potential antipsychotics (35).

Schizophrenic patients have deficits in PPI (8,9) and are less responsive in another test of gating that measures the evoked response to the second of a pair of auditory stimuli (termed the P-50 wave) (4,5,23). In the rat, an analogous measure of this latter form of gating is demonstrated by recording the evoked response (P-40 wave) from the CA3 region of the hippocampus. Amphetamine treatment (7) impairs gating in this model. The observed deficits in gating could be a reflection of attentional disorders observed in schizophrenic patients (33).

Apomorphine, a dopamine agonist, has been shown to disrupt PPI when the difference between the prepulse (PP) and background intensities are small, with the inference that apomorphine is affecting the "detectability of the prepulse" (18). These effects at low levels of PP could possibly be a reflection of altered attention. Subsequent studies have revealed that the dopamine antagonists clozapine and haloperidol are able to reverse the effects of apomophine on PPI, and low doses of clozapine alone increases PPI following a weak PP stimulus (less than 5 dB over background) (36).

Nicotine, which increases attentional measures in humans (28), also improves gating measures in first and second degree relatives of schizophrenic patients following nicotine treatment (4). There is also evidence that α-bungarotoxin, but not mecamylamine or scopolamine, injected intraventricularly decreases the gating response to the auditory evoked potential P-40 wave in the rat (29), suggesting a subset of nAChRs that have α-bungarotoxin sites in the hippocampus may be involved in sensory detection.

The role of other neurotransmitters, including the cholinergic system, in gating has been less well studied. There has been a report of biphasic effects on PPI following nicotine

[1] To whom requests for reprints should be addressed.

treatment (3). We tested the effects of (−)-nicotine, and the nAChR channel blocker mecamylamine in this model. (−)-Lobeline, which binds at nAChRs with similar affinity as nicotine (1,24,34), was also tested because in contrast to (−)-nicotine, it has minimal effects on dopamine release (24,40).

METHOD

One hundred and nineteen Long-Evans male rats (225-250 g) from Charles River Labs, Portage, MI. were used. They were singly housed in a climate-controlled environment with ad lib food and water. Illumination was provided between 0700-1900 h. Testing was conducted between the hours of 0900-1500 h.

Four startle chambers (SR-LAB, San Diego Instruments, San Diego, CA) were employed. The rat was placed in a Plexiglas cylinder (8.2 cm in diameter × 12.0 cm long) attached to a rigid frame, contained in a sound deadening, lighted, ventilated enclosure. Background noise and acoustic stimuli were delivered from a loud speaker directly above the rat. Startle responses, reflected by each rat's movement immediately following the auditory stimulus, were measured for a period of 100 ms, by a piezoelectric cartridge attached to the underside of the cylinder, output from which was converted into a digital record by the interface. A HP Vectra computer controlled the timing of the stimuli and recorded the data output. Sound levels were calibrated by a Radio Shack Sound Level Meter #33-2050 on slow response, "A" weighting.

Habituating Sessions

Rats were placed into the chambers for two sessions on consecutive days. The chambers were lighted and a 65 dB background noise was present. Following a 5-min habituation period, each rat was subjected to 30 acoustic startle trials, 10 trials each at 90, 95, and 105 dB noise of 30 ms duration. A 30 s variable intertrial interval separated each trial (mininum, 5 s; maximum, 45 s). The mean maximal response to the 105 dB stimulus on the second day was used to match the animals into balanced groups for drug testing.

Drug Sessions

Following a 5-min habituation with a 65 dB background noise, six different test trials were used; a) 120 dB, 40 ms noise burst; b) prepulse trials in which the 120 dB 40 ms noise was preceded by 100 ms with a 20 ms noise burst of either 5, 10, and 15 dB above background (70, 75, or 80 dB); c) 105 dB 40 ms trial; and d) a recording taken when no noise was presented. Eight trials of each type were presented in quasirandom order with a 15 s variable intertrial interval (minimum 5, maximum, 30). All drug treatments were administered intraperitoneally (1.0 ml/kg) 15 min prior to the start of the PPI session. A vehicle injection of 0.9% saline was used as a control.

To test (−)-nicotine (0.19, 0.62, and 1.9 μmol/kg) (equivalent to 0.03, 0.1, and 0.3 mg/kg base), 16 animals were used in a crossover design (quasi-Latin square). One-half the animals received the treatments in ascending order while the other half received a descending order. Four animals were started at each treatment level to eliminate any order effect for drug treatment. Drug sessions were separated by 3 days.

In the other experiments, a between-animal design was used in which each subject was only tested once. Effects of two doses of mecamylamine were tested (5.0 and 50.0 μmol/kg, n = 8/group) (equivalent to 1.0 and 10.0 mg/kg). Four doses of (*l*)-lobeline were tested (0.19, 0.62, 1.9, and 6.2 μmol/kg n = 10/group) (equivalent to 0.071, 0.23, 0.71, 2.3 mg/kg). Mecamylamine blockade of nicotine effects was assessed by treating rats with mecamylamine (5.0 μmol/kg) 15 min before they received an injection of nicotine (0.19 and 0.62 μmol/kg, n = 10/group).

The mean maximal startle response was analyzed as well as the percent of prepulse inhibition. For data analysis, the prepulse inhibition percentage is calculated as the (mean maximal response to 120 dB nonprepulse trials alone, minus the mean maximal response to 120 dB on prepulse trials, divided by the mean maximal response on the 120 dB non prepulse trials) × 100. Analysis of variance (ANOVA) was used where appropriate with post hoc comparisons using Fisher's protected least significance difference test.

Drugs

(−)-Nicotine hydrogen bitartrate, mecamylamine hydrochloride, and (−)-lobeline hydrochloride were obtained from Sigma Chemical Co., St. Louis, MO. All drugs were prepared in 0.9% saline solution immediately before treatment.

RESULTS

Analysis of all the data revealed no effects of (−)-nicotine, mecamylamine or (−)-lobeline treatment on the amplitude of the mean startle response to 120 dB startle alone trials, as shown in inserts of Figs. 1, 2, and 4.

The effects of (−)-nicotine are illustrated in Fig. 1. The

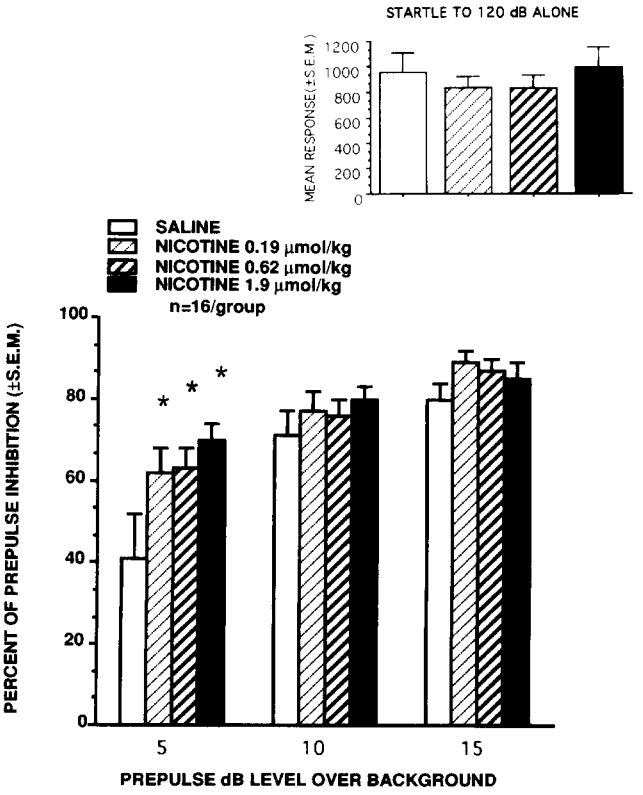

FIG. 1. Effects of IP (−)-nicotine on prepulse inhibition at three stimulus intensities. At all doses of nicotine there was a significant (*) decrease in PPI $p < 0.03$ ANOVA at the 70 dB level.

overall effect of nicotine significantly [nicotine main effect, $F(3, 45) = 3.119$, $p = 0.035$] increased prepulse inhibition. There was no interaction between PP levels × dose nicotine, $F(6, 90) = 1.693$, $p = 0.13$, although subsequent one-way ANOVA factorial analysis revealed that the nicotine effects were observed at the 5 dB level of PP, $F(3, 60) = 3.116$, $p = 0.0327$, but not at the 10 dB, $F(3, 60) = 0.59$, $p = 0.62$, or the 15 dB level, $F(3, 60) = 1.324$, $p = 0.275$. Post hoc analysis revealed that all doses significantly enhanced PPI at the 5 dB prepulse level.

Mecamylamine treatment (Fig. 2) produced a significant dose effect on the ANOVA, $F(2, 21) = 5.688$, $p = 0.011$, and no dose × PP levels interaction, $F(4, 42) = 0.445$, $p = 0.776$. The lowest dose 5.0 μmol/kg was ineffective, while the higher dose (50.0 μmol/kg) of mecamylamine significantly reduced PPI ($p < 0.05$).

In a separate experiment (Fig. 3) assessing the effects of mecamylamine (5.0 μmol/kg) pretreatment on nicotine, there was no significant main effect of mecamylamine on PPI, $F(1, 54) = 0.993$, $p = 0.323$. There was a significant nicotine main effect, $F(2, 54) = 6.549$, $p = 0.003$, with no nicotine × mecamylamine interaction, $F(2, 54) = 0.643$, $p = 0.53$. Subsequent analysis using a two-way ANOVA at each of the PP levels revealed a significant increase of PPI by nicotine at the 5 dB, $F(2, 54) = 7.076$, $p = 0.0019$, and at the 10 dB, $F(2, 54) = 3.653$, $p = 0.033$, but not at the 15 dB level, $F(2, 54) = 2.061$, $p = 0.14$. Post hoc analysis of this nicotine main effect revealed that both doses of nicotine were effective at 5 dB PP level, and nicotine 0.62 μmol/kg was effective at 10 dB PP level.

There was no effect of (−)-lobeline treatment (Fig. 4), [lobeline main effect, $F(4, 44) = 0.715$, $p = 0.586$, and lobeline × PP level interaction, $F(8, 88) = 3.82$, $p = 0.928$].

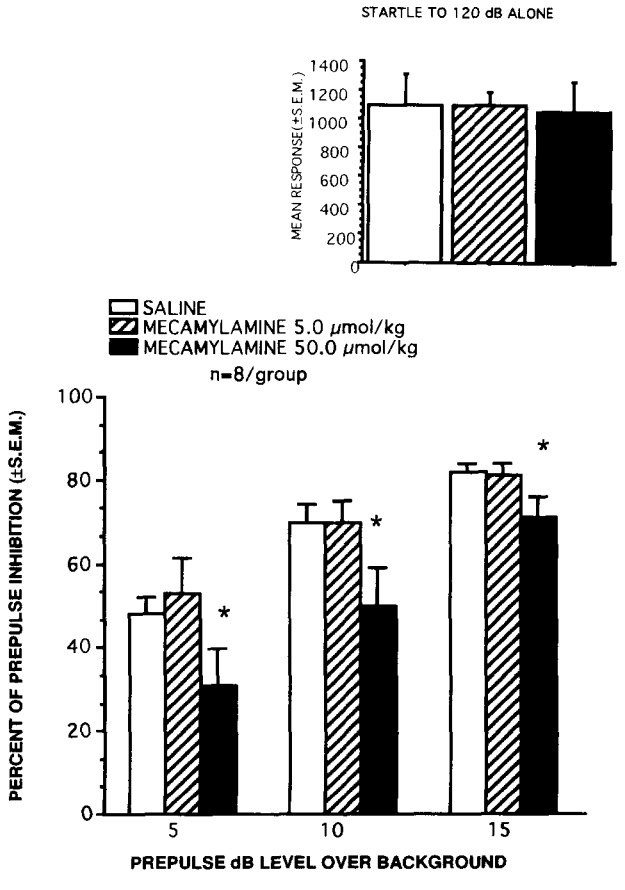

FIG. 2. Effect of mecamylamine on prepulse inhibition. Mecamylamine 50.0 μmol significantly (ANOVA drug × levels $p = 0.01$ increased the PPI at all the PPI stimulus levels, (*) Fisher $p < 0.05$.

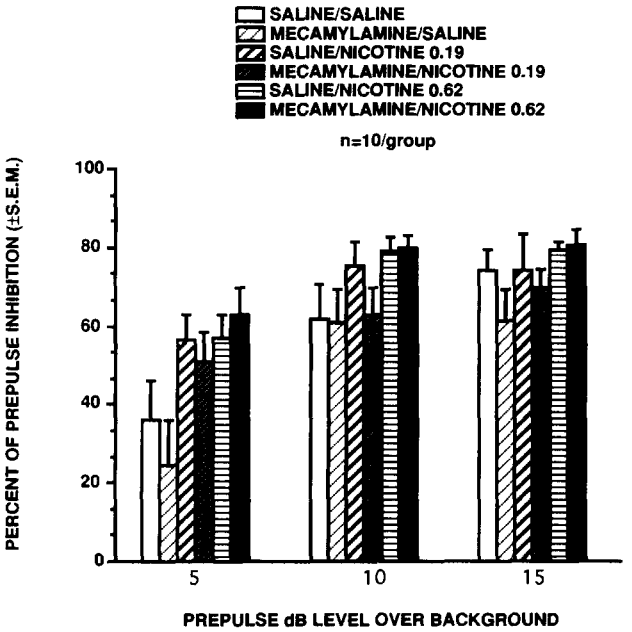

FIG. 3. Effects of mecamylamine 5.0 μmol/kg on (−)-nicotine increase of PPI. There was a significant overall nicotine effect three-way ANOVA $p < 0.001$. Subsequent two-way ANOVA produced a significant effect of nicotine treatment for the 0.62 μmol/kg at the 5 and 10 dB levels and significant effect of 0.19 μmol nicotine at 5 dB PP. There was no mecamylamine effect or interaction with nicotine.

DISCUSSION

Our data clearly show no differences in startle amplitude following nicotine or mecamylamine treatment, which eliminates any difficulties in interpreting the PP data associated with changes in baseline response magnitude. This is different from a previous report in which chronic nicotine has been shown to increase acoustic startle response in rats (2). This inconsistency may be a result of strain and dosing differences as the increase in startle amplitude following acute and chronic nicotine in mice is strain dependent (16).

These results show that nicotine increased PPI in the rat when lower levels of prepulse were employed. There was not a significant increase in PPI at the highest PP intensities, although the direction of the change was to increase PPI. One interpretation of the enhanced PPI at the lower PP levels could be that the nicotine is affecting the detectability of the PP, an effect that would be most prominent at lower PP levels or, alternatively, the lack of effect at higher PP levels could be the result of a ceiling effect.

A decrease in PPI is observed at all PP levels following treatment with the higher dose of mecamylamine 50.0 μmol/kg, but not with the lower (5.0 μmol/kg) dose. Mecamylamine does not bind at the nicotine binding site but blocks the nAChR channel. The fact that PPI decreases following ad-

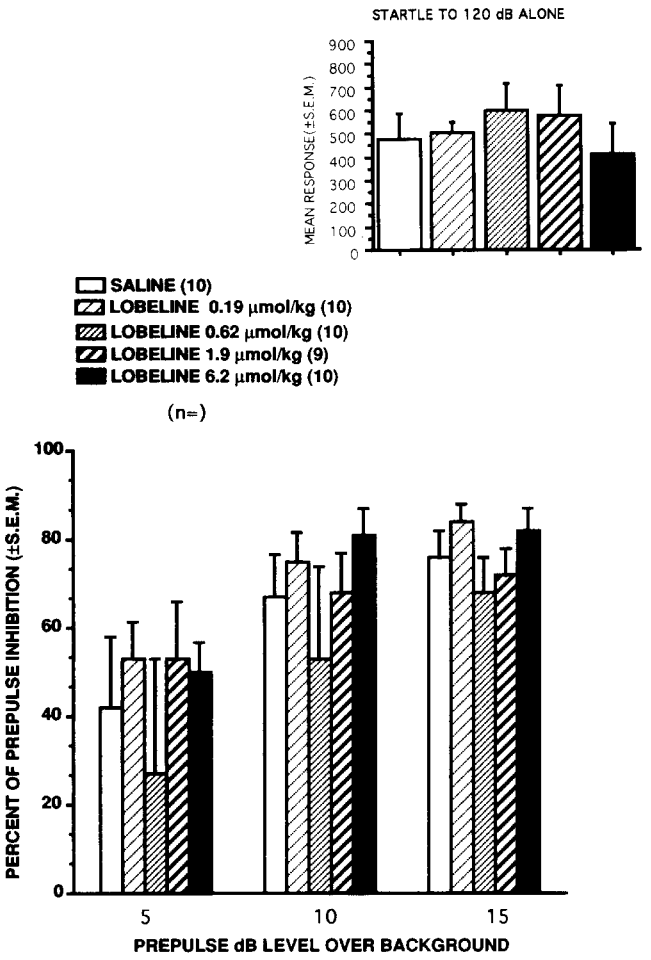

FIG. 4. Effect of (−)-lobeline on PPI at three stimulus intensities. Lobeline was ineffective at all prepulse levels.

ministration of 50.0 μmol/kg mecamylamine could be due to effects at the NMDA receptor as high doses of mecamylamine can block NMDA receptor function as discussed by Clarke and Fibiger (14). Consistent with this interpretation MK-801, an NMDA receptor antagonist, has been shown to decrease PPI (30), although this effect may be reflective of an interaction at the PCP receptor.

When the nicotine/mecamylamine interaction was studied, mecamylamine (5.0 μmol/kg) was without effect on PPI. Furthermore, this dose of mecamylamine failed to reverse the increase in PPI following acute nicotine treatment. Again, nicotine treatment increased the PPI when lower PP levels were used. Previous work in this laboratory has established that mecamylamine, at the dose tested, blocks nicotine-induced (up to 1.9 μmol/kg) enhancement of inhibitory avoidance and nicotine's locomotor effects (up to 6.2 μmol/kg) (19). Also, this dose of mecamylamine is sufficient to block nicotine-induced changes in baseline startle when changes are present in mice (15). Thus, the dose of mecamylamine used here is sufficient to block other behavioral effects of nicotine.

(−)-Lobeline is a nicotinic agonist with minimal effect on dopamine release (24,40) that has been shown to share some of the behavioral effects of nicotine on cognitive tasks (20). Treatment with (−)-lobeline was ineffective in this paradigm at all of the prepulse levels. We tested (−)-lobeline 10 times the effective dose for (−)-nicotine without any indication of an increase in PPI. (−)-Lobeline has lower binding affinity than nicotine for the α-bugarotoxin site, and little is known about its efficacy at this site (32). Therefore, at these doses, (−)-lobeline may not be acting at receptors responsible for the nicotine induced increases in PPI.

Nicotine treatment increases the release of dopamine in the nucleus accumbens (6,26) and striatum (17) as well as increasing extracellular levels of noradrenaline and dopamine metabolites in the hippocampus (10). Evidence for dopaminergic involvement in PPI in the rat has shown that DA agonists will decrease PPI (18,37) and DA antagonists will increase PPI (36). The release of dopamine and noradrenaline is blocked by mecamylamine (10). Therefore, if nicotine-induced catecholamine release is responsible for the effects in the present experiments, nicotine treatment would cause a decrease in PPI, and also would be blocked by the mecamylamine pretreatment, neither of which occurred. There is obviously a role of dopamine in the PPI. However, this role appears to be separate from the nicotinic effects on gating found in the current study.

Further evidence for the involvement of cholinergic systems in gating comes from studies on the effects of carbachol. Infusion of carbachol, a mixed nicotinic/muscarinic agonist, into the hippocampus, an area that has been implicated in sensorimotor gating, results in a decrease in PPI (11,12). This effect is blocked by the muscarinic antagonist atropine, suggesting that this cholinergic disruption of PPI involves stimulation of muscarinic receptors. However, muscarinic effects are confusing because peripheral administration of the muscarinic antagonist scopolamine also reduces PPI (42).

A role for the hippocampus in gating has been established (7,12,29). Evidence for involvement of nicotinic neurotransmission in gating may be derived from the fact that nicotine increases the response to the P-50 wave in first- and second-degree relatives of schizophrenics who had a deficit in this response (4). In rat studies, reduction of choline levels by the use of *N*-aminoamidol treatment resulted in an increase in the startle threshold but a decrease in PPI (42). This reduction in PPI was partially reversed by the mixed nicotinic/muscarinic agonist arecoline. Notably, arecoline binds with high affinity to the nAChR, and a nicotinically mediated enhancement of PPI in this model would be consistent with the present finding that nicotine enhances PPI in normal rats.

There are many known subtypes of the nicotinic receptor (13,21) found in various densities within the layers of the hippocampus and other brain areas (25,38). Nicotine has been shown to bind with high affinity (K_i = 1 nM) to the α4-β2 subtype stably expressed in transfected cell lines (41). This subtype is thought to constitute greater than 90% of the high affinity (−)-nicotine binding sites in rodent brain (22). In contrast, (−)-nicotine has lower affinity (K_i > 1 μM) for the α-bugarotoxin binding site in the whole brain. In the auditory evoked response rat model, α-bungartoxin disrupts gating and mecamylamine is ineffective (29). If mecamylamine is ineffective at the α-bugarotoxin site and nicotine reverses a gating deficit in humans, then it follows that the nicotine effects in this model of gating that are not blocked by mecamylamine could be the result of effects on the α-bungartoxin receptor site. The present data showing a nicotine-induced increase in PPI at low PP levels, and no blockade with mecamylamine is consistent with the interpretation that these effects involve α-bungarotoxin sites.

The results contained in these experiments would certainly point to a role for the α-bungarotoxin site in the action of nicotine on PPI. With the availability of methyllycoconitine (MLA), a selective ligand for the α-bungarotoxin sensitive nAChR (21,39), future experiments would assess the ability of MLA to block the nicotine effects.

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