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Normalizing Effects of Nicotine and a Novel Nicotinic Agonist on Hippocampal Auditory Gating in Two Animal Models

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STEVENS, K. E. AND K. D. WEAR. *Normalizing effects of nicotine and a novel nicotinic agonist on hippocampal auditory gating in two animal models.* PHARMACOL BIOCHEM BEHAV **57**(4) 869–874, 1997.—Rapid habituation of the evoked response to repeated auditory stimuli is a physiological manifestation of sensory gating mechanisms that are disturbed in human psychoses. Similar deficits are found in two animal models: fimbria-fornix lesioned Sprague–Dawley rats and DBA/2 mice, an inbred strain with decreased numbers of hippocampal $\alpha 7$ nicotinic receptors. In response to paired auditory stimuli, the hippocampal evoked response of outbred, unlesioned animals is larger to the first than to the second stimulus. Both fimbria-fornix lesioned rats and DBA/2 mice have decreased response to the first stimulus but no further suppression of response to the second stimulus. Parenteral administration of (*S*)-3-methyl-5-(1-methyl-2-pyrrolidinyl) isoxazole (ABT418), a newly developed nicotinic agonist, was found to normalize hippocampal auditory evoked responses in both models. The response to the first stimulus was increased, and the response to the second stimulus was suppressed relative to the first. The magnitude and time course of effect were similar to those observed with a 10-fold greater dose of nicotine. Both nicotine and ABT418 were ineffective when a second dose was administered 1 h later, suggesting that both compounds may desensitize the receptor mechanism. © 1997 Elsevier Science Inc.

Nicotinic receptors Cholinergic receptors Hippocampus Habituation Auditory system DBA inbred mice

THE cholinergic afferents to the hippocampus from the medial septal nucleus have long been thought to play a critical role in the ability to perform tasks involving orientation and short-term memory (6). For example, rats with lesions that disrupt the cholinergic pathway from the medial septal nucleus and diagonal band of Broca to the hippocampus perform poorly on the Morris water maze (19). Such lesions also impair more elementary neurophysiological functions of hippocampal neurons, namely the rapid habituation of hippocampal neurons to repeated auditory stimuli (33). This habituation may subserve a sensory gating function to allow the animal to ignore noisy, repetitive features of the environment so that attention can be directed to more novel features.

Nicotinic cholinergic modulation of the gating function has been demonstrated by normalization of amphetamine-induced loss of gating by nicotine administration (32). The critical nicotinic receptor for this gating function appears to be an α-bungarotoxin sensitive receptor (26) that is found on hippocampal pyramidal cells and interneurons (22). Neither muscarinic antagonists, such as scopolamine, nor nicotinic ganglionic and neuronal antagonists, such as mecamylamine, affect this sensory gating function. This pharmacology was initially demonstrated using an auditory evoked potential, the P20–N40 complex, recorded from the CA3 pyramidal layer of the rat hippocampus in response to paired tones. Normally, the amplitude of the response to the second tone is less than 40% of that to the first tone. α-Bungarotoxin, but not κ-bungarotoxin (neuronal bungarotoxin), decreased the response to the first tone and the suppression of response to the second tone. A similar pharmacology has recently been observed with another sensory gating measure, the inhibition of the acoustic startle response by a prepulse tone (11). An additional piece

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of evidence that points to the role of hippocampal α-bungarotoxin receptors is that inbred mice of the DBA/2 strain, which have reduced numbers of these receptors, have diminished inhibitory gating of their hippocampal evoked response to repeated auditory stimuli (31).

The relevance of these mechanisms to humans has been suggested by a series of experiments that show that: a) schizophrenic patients have diminished sensory gating (3), and b) such sensory gating deficits can be transiently reversed by nicotine (1). Sensory gating deficits have been demonstrated in schizophrenics with a variety of paradigms, including smooth pursuit eye movements, prepulse inhibition of acoustic startle, and inhibition of the P50 auditory evoked response in a paired stimulus or conditioning–testing paradigm (8). Deficits in smooth pursuit eye movements and diminished inhibition of the P50 evoked response are both improved after the subject takes nicotine, either by chewing nicotine-containing gum or by smoking cigarettes (2). Schizophrenics have long been known to be particularly heavy smokers, a behavior that has been suggested to be a form of self-medication (18).

These findings raise the question of whether other nicotinic agonists could be substituted for cigarette smoking to supplement current drug treatments for schizophrenia. Classical neuroleptics primarily block catecholaminergic neurotransmission and, although effective, nevertheless do not alleviate all the symptoms of schizophrenia (16), nor do they normalize smooth pursuit eye movements or P50 inhibition. Thus, nicotinic agonists might eventually have a significant therapeutic role in schizophrenia. Cigarette smoking itself has the obvious problem that it introduces carcinogenic by-products such as tar into the body. An additional problem with cigarette smoking is the brief period of effect. Whether the brief effect reflects the fast pharmacokinetics of smoke inhalation or the rapid desensitization of α-bungarotoxin sensitive receptors, as has been demonstrated with the α7 nicotinic subunit homooligomer (29), is unknown.

ABT418 is a recently developed nicotinic agonist that is significantly more potent than nicotine in animal paradigms related to anxiolytic and memory enhancement effects, but is less potent in producing hypothermia, seizures, bradykinesia, and death (12). It normalizes the increase in motor activity caused by medial septal lesion and retains its anxiolytic effect after 14 days of administration. Thus, the findings of less toxicity and the possibility of less desensitization make it a promising candidate as an alternative to nicotine for psychotic patients. The purpose of the present study was to examine its efficacy in two animal models of sensory gating abnormality, the fimbria-fornix lesioned Sprague–Dawley rat and the DBA mouse.

METHODS

Male Sprague–Dawley rats, 200–400 g, were procured from Harlan Laboratories. DBA/2 mice, 20–30 g, both male and female, were obtained from Jackson Laboratories.

The rats were anesthetized with secobarbital [40 mg/kg intraperitoneally (IP)]. Under aseptic conditions, a burr hole was opened 1.0 mm posterior to bregma and 0.5–4.0 mm lateral to the midline. The overlying cerebral cortex and the underlying fimbria-fornix pathway were aspirated. The skull defect was closed with gelfoam and bone wax. The skin was closed over the skull, and the animals were allowed to recover for 1–2 weeks. In a previous study, animals lesioned with this procedure had over 90% depletion of choline acetyltransferase (ChAT) in the hippocampus. A second series of animals in that study received only lesions of the cerebral cortex overlying the fimbria-fornix. These animals had normal hippocampal electrophysiology (7). In the present study, the completeness of the fimbria-fornix lesions was evaluated by determination of ChAT enzyme activity by the method of Fonnum (14). Verification of efficacy of the lesion has been reported elsewhere (7). Briefly, hippocampal tissue from the fimbria-fornix lesioned rats showed 96.4 ± 1.03% depletion in ChAT activity as compared with equivalent hippocampal tissue from other nonlesioned rats.

For electrophysiological recording, both rats and mice were anesthetized with chloral hydrate (400 mg/kg IP) and pyrazole (400 mg/kg IP) to retard the metabolism of the chloral hydrate. The rats were intubated and placed in a stereotaxic apparatus; a heating pad maintained body temperature at 32°C. The stereotaxic apparatus had hollow earbars that were connected to miniature earphones. The mice were not intubated, and their body temperature was maintained at 31°C. The mice were fixed by the nose clamp of a special mouse adaptor (Neuroprobe, Cabin John, MD, USA); the hollow earbars were placed adjacent to, but not inserted into, the auditory meatus. Anesthesia was supplemented periodically to maintain absence of reflexive withdrawal from toe pinch.

For both rats and mice, a burr hole was made over the CA3 region of hippocampus ipsilateral to the fimbria-fornix lesion side for the rats. A tungsten microelectrode, impedance 8–10 megohms at 1000 Hz, was inserted into the CA3 pyramidal layer of the hippocampus. The location of the electrode was estimated by its depth from the brain surface; final location was identified by the presence of complex action potentials typical of hippocampal pyramidal neurons. The electrical activity was amplified 1000 times with bandpass 1–500 Hz and led to an analog to digital converter (RC Electronics, Bakersfield, CA, USA) for averaging by an Apple IIe computer.

Tones (3000 Hz, 10 ms, 70 dB SPL) were presented in pairs, with a 0.5-s intrapair interval and 10 s between pairs. Responses to 16 pairs were averaged at 5-min intervals. Each average was filtered digitally with bandpass between 10 and 250 Hz. The maximum negativity between 20 and 60 ms after the first stimulus was selected as the N40 wave and measured relative to the preceding positivity, a P20 wave (10). This particular complex has greater reproducibility for repeated measurements than either component alone. Agonists were administered after a baseline of three measurements. Two sequential doses of agonist or saline were administered in DBA/2 mice, 40 min apart. For antagonist experiments in mice, 0.5 μl of antagonist was injected directly into the anterior lateral ventricle over a 30-s period. Five minutes following antagonist administration, one recording was made, after which the agonist was administered. Preplanned comparisons of maximum ABT418 drug effect with baseline were performed by Student's *t*-test for the fimbria-fornix lesioned rats. The time course of effect of the two sequential administrations of nicotine or ABT418 to DBA/2 mice was compared using multiple analysis of variance (MANOVA), followed by Tukey–Kramer a posteriori analyses.

RESULTS

Effects of ABT418 in Fimbria-Fornix Lesioned Rats

As previously observed, fimbria-fornix lesioned rats showed a decreased conditioning P20–N40 response, as well as loss of inhibitory gating of this auditory evoked response. The mean conditioning amplitude was 0.55 ± 0.08 mV, and

the ratio of the test to the conditioning amplitude was 1.18 ± 0.27. Figure 1 shows sample waveforms recorded in this paradigm. In comparison, the unlesioned animals had a mean conditioning amplitude of 1.0 ± 0.3 mV, and the ratio of the test to the conditioning amplitude was 0.26 ± 0.09. A comparison of lesioned vs. unlesioned animals showed a significant loss of gating for lesioned animals (two-tailed Student's *t*-test, df = 16, $p < 0.01$). Administration of ABT418 [0.062 μmol/kg subcutaneously (SC)] increased the conditioning P20–N40 amplitude in the fimbria-fornix lesioned rats to 0.90 ± 0.20 mV 30 min after administration. This effect was a significant increase over the pretreatment level ($t = 3.98$, df = 4, $p < 0.05$). The ratio of the test to the conditioning amplitude decreased after ABT418 administration to 0.36 ± 0.17 ($t = 5.14$, df = 4, $p < 0.05$). This effect of ABT418 was lost after 1 h. A second administration of the same dose had no effect on the gating of P20–N40, but the effect could be restored with a 10-fold higher dose. In the unlesioned rats, ABT418 caused a slight, nonsignificant decrease in the conditioning amplitude, which produced a small, nonsignificant increase in the ratio of the test to the conditioning amplitude (Fig. 2).

Effects of ABT418 and Nicotine in DBA/2 Mice

DBA/2 mice also failed to suppress the amplitude of the P20–N40 response to the second of paired auditory stimuli, as previously observed. The mean ratio of the test to the conditioning amplitude before injection of drugs or vehicle ranged from 1.10 ± 0.12 to 1.07 ± 0.07. The initial administration of either ABT418 (0.062 μmol/kg SC) or nicotine (6.4 μmol/kg SC) significantly increased the conditioning amplitude and decreased the ratio of the test to the conditioning response relative to either unmedicated baseline or to vehicle control responses (Figs. 3, 4). For the conditioning amplitude, MANOVA comparing ABT418 or nicotine with vehicle control showed a significant interaction of time of recording and drug administration after the first injection [$F(9, 99) = 2.02$, $p = 0.05$ and $F(9, 99) = 2.31$, $p = 0.02$, respectively]. Tukey's

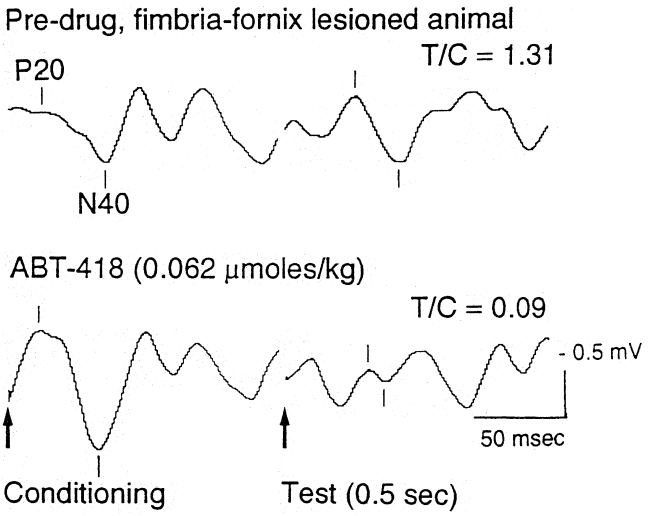

FIG. 1. Effects of ABT418 (0.062 μmol/kg SC) on the hippocampal evoked response to repeated auditory stimuli (arrows) in a fimbria-fornix lesioned Sprague–Dawley rat. The ratio of the test to conditioning P20–N40 amplitudes (T/C) is shown. The tic marks above and below the traces identify P20 and N40, respectively. Vertical calibration is −0.5 mV horizontal is 50 ms.

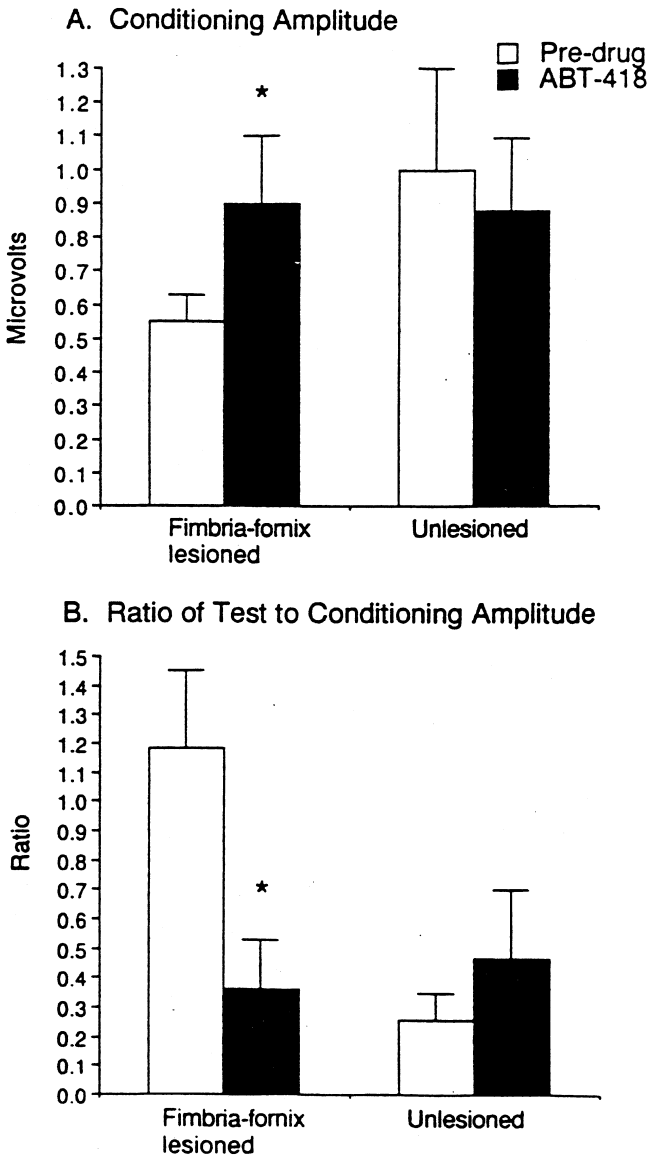

FIG. 2. Effects of ABT418 (0.062 μmol/kg SC) on (A) conditioning amplitude and (B) test to conditioning ratio, in fimbria-fornix lesioned Sprague–Dawley rats ($n = 5$) and unlesioned rats ($n = 5$). Mean and standard error are shown. *$p < 0.05$ by paired *t*-test comparing predrug with post-ABT418 values.

HSD a posteriori analyses showed significantly greater amplitude from 10 to 30 min after the first administration of either drug but no significant change at any other time.

For the ratio of the test to the conditioning response, MANOVA also showed a significant interaction between drug choice and time of recording [$F(34, 289) = 1.55$, $p = 0.03$]. Tukey's HSD a posteriori analysis showed significantly lower ratios 10–25 min after the first administration of the drugs but no significant response at any other time. Thus, a second dose of either nicotine or ABT418, administered 40 min after the first dose, when the evoked potential amplitude and ratio had returned to baseline levels, had no significant effect on either conditioning amplitude or the ratio of the test to the conditioning amplitude.

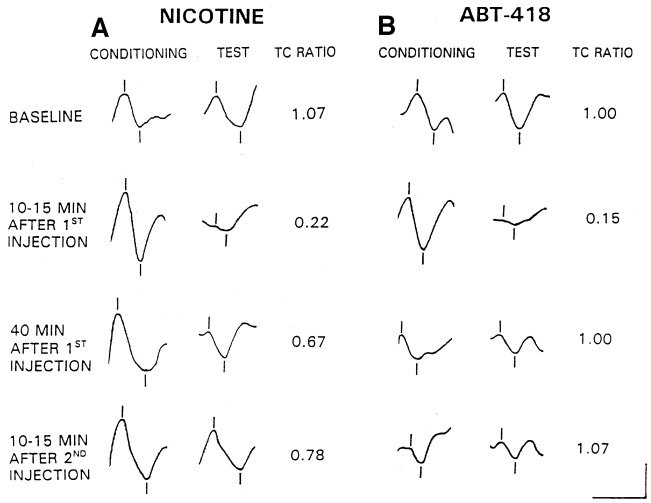

FIG. 3. Examples of hippocampal evoked potentials recorded from DBA/2 mice. One received 6.4 μmol/kg nicotine; the other received 0.062 μmol/kg ABT418. Baseline data and the response to the drugs are shown. There was no response to a second dose of either drug administered 1 h after the first. The tic marks above and below the traces identify P20 and N40, respectively. Vertical calibration is −0.5 μV horizontal is 50 ms.

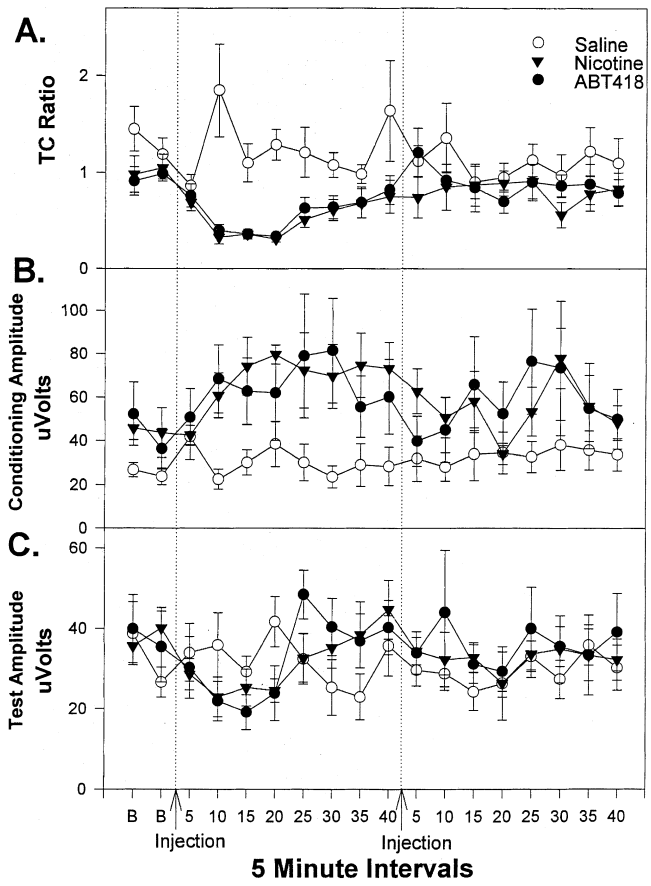

FIG. 4. (A) Ratio of test to conditioning amplitude (TC ratio); (B) amplitude of the conditioning response; and (C) amplitude of the test response for DBA/2 mice during predrug baseline and after two administrations of saline (n = 6), nicotine (6.4 μmol/kg SC; n = 7), or ABT418 (0.062 μmol/kg SC; n = 7). Data are mean ± SEM; injections were made at the times noted with arrows.

The change in conditioning amplitude and the change in ratio between baseline and peak drug effect, 20 min after the first administration, were correlated (r = 0.58, $p < 0.03$). There were no significant effects of either drug on the amplitude of the test response [$F(34, 289) = 0.98, p = 0.51$].

Administration of α-bungarotoxin [0.5 μl of 200 nM (100 fmol) intracerebroventricularly (ICV)] prior to ABT418 completely blocked the normalization of gating that had been observed with ABT418 alone (Fig. 5). In contrast, administration of mecamylamine [0.5 μl of 200 μM (100 pmol) ICV] prior to ABT418 had no effect on the normalization of gating by the agonist (Fig. 5).

DISCUSSION

ABT418 was developed as an agonist for the receptors that bind acetylcholine, nicotine, and cytisine with high affinity (5). These receptors appear to be composed primarily of α4 and β2 subunits in the rat brain (14), but other subunit compositions are also possible (25). Receptors that bind the antagonist α-bungarotoxin also bind these agonists but with significantly lower affinity (4). These lower affinity receptors have a distribution in the brain different from the higher affinity receptors, which led to some question as to whether the so-called toxin receptor was indeed involved in neurotransmission (9). The cloning of this receptor, the α7 subunit, led to the demonstration that it indeed could form an ion-gated ligand channel (29). The very rapid desensitization of this receptor may have obscured earlier identification of its functional role.

The goal of the present study was to determine if ABT418 would affect functions related to the α-bungarotoxin sensitive receptor when administered at parenteral doses comparable to those showing effects in other behavioral paradigms. There are in vitro models that demonstrate the activity of this receptor at the membrane channel level, but there are only two functional demonstrations at the whole animal level. The sensitivity to nicotine induced seizures has been shown by genetic correlation to be related to the number of hippocampal α-bungarotoxin sensitive receptors (27). The evidence that the α-bungarotoxin sensitive receptor is critical in the inhibitory gating of the hippocampal response to auditory stimuli was outlined in the introduction. Both of these functions implicate an interaction between this receptor and inhibitory activity in the hippocampus, a relationship supported by the finding that these receptors are particularly dense on a subpopulation of GABAergic hippocampal interneurons in the rat (17).

A number of investigations have also demonstrated effects of cholinergic agonists on hippocampal neurotransmission (15,20,28). However, comparison of a full range of muscarinic and nicotinic agonists and antagonists was not generally performed in these experiments, so the receptor subtypes involved cannot be rigorously specified. In other brain areas involved in the nonlemniscal processing of sensory input, e.g., the brain stem reticular formation, the cholinergic receptors have a pharmacology similar to the sensory gating response in the hippocampus, i.e., sensitivity to neuromuscular-type antagonists (30).

ABT418 normalized the inhibitory gating of hippocampal auditory evoked response in two different animal models, one of which is produced by lesion of presynaptic cholinergic neu-

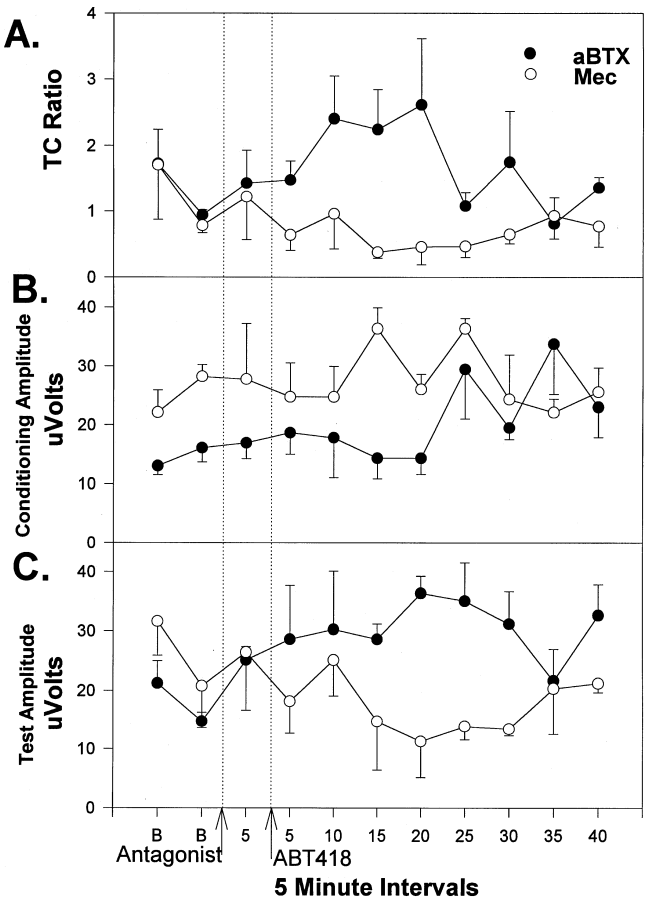

FIG. 5. (A) Ratio of test to conditioning amplitude (TC ratio); (B) amplitude of the conditioning response; and (C) amplitude of the test response for DBA/2 mice during predrug baseline, after ICV injection of α-bungarotoxin [aBTX; 0.5 μl of 200 nM (100 fmol)] or mecamylamine [Mec; 0.5 μl of 200 μM (100 pmol)], and after a subsequent SC injection of ABT418 (0.062 μmol/kg SC). Antagonist injection was made at the time noted by the first arrow; ABT418 was administered at the time noted by the second arrow. Data are mean ± SEM; $n = 3$ for each group.

rons and the other of which is produced by genetic changes in the expression of the α-bungarotoxin sensitive receptor. In both cases, ABT418 increased the amplitude of the initial or conditioning P20–N40 wave and also increased the suppression of the second or test response. α-Bungarotoxin in unlesioned animals has exactly the opposite effect: it decreases the conditioning amplitude and decreases the suppression of the test response (26). These two parameters are not necessarily correlated; for example, $GABA_B$ antagonists decrease suppression of the test response but do not decrease conditioning amplitude in this paradigm (21). The correlation between the two effects may reflect the presence of α-bungarotoxin sensitive receptors on the pyramidal neurons as well as the interneurons (22). Thus, activation of the receptors on the pyramidal neurons would increase the conditioning response, whereas activation of the receptors on the interneurons would increase suppression of the test response.

Co-administration of antagonists with ABT418 further suggests activity of this agonist at α-bungarotoxin sensitive receptors. Central injection of α-bungarotoxin blocked the improvement in inhibitory gating observed with ABT418 in DBA/2 mice, whereas administration of mecamylamine did not.

The results of this study suggest that ABT418 might have effects on sensory gating deficits in humans similar to those found with nicotine. Whether these effects would have therapeutic importance remains to be determined. For schizophrenics, heavy smoking has been correlated with poor prognosis; some patients smoke so much that the nicotine interferes with their ability to regulate serum osmolality, presumably because of its effects on the subfornical organ (24). However, their heavy smoking may reflect the neurobiology of their poor prognosis rather than contribute to it. Clinical anecdotal evidence suggests that smoking is an effective short-term remedy for psychotic agitation, but there seems to be no long-term beneficial effect of smoking on the course of schizophrenia. Attempts to prolong the benefit by transdermal slow release nicotine administration have not been successful with schizophrenics, because they continue to smoke despite such treatment, suggesting that they seek the higher nicotine doses provided by cigarettes (23).

ABT418 was equally effective with nicotine at the doses administered in the experiments described here and has a similar pattern of desensitization. The desensitization would give ABT418 little advantage over nicotine in terms of the development of a longer term treatment. On the other hand, it may be that receptor desensitization is what schizophrenic smokers seek when they repeatedly inhale cigarettes. In either case, ABT418 would merit further investigation as a therapeutic agent because of its better side effects profile.

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