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Galantamine and Donepezil Attenuate Pharmacologically Induced Deficits in Prepulse Inhibition in Rats

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Abstract

Acetylcholinesterase inhibitors (AChEIs) are currently being evaluated as adjunctive therapy for the cognitive dysfunction of schizophrenia. This core symptom of schizophrenia has often been attributed to impaired attention and abnormal sensory motor gating, features that are also found in Huntington's Disease, autism, and several other psychiatric and neurological disorders. The ability to improve prepulse inhibition (PPI) of the acoustic startle response may predict the efficacy of compounds as cognitive enhancers. In this study, PPI was disrupted in Wistar rats in three pharmacologic models: dopamine receptor agonism by apomorphine, NMDA receptor antagonism by MK-801, or muscarinic acetylcholine receptor antagonism by scopolamine. We then evaluated the commonly used AChEIs, donepezil (0.5, 1.0, or 2.0 mg/kg) and galantamine (0.3, 1.0, or 3.0 mg/kg) for the capacity to improve PPI in each model. Under vehicle conditions, the prepulse stimuli (75, 80 and 85 dB) inhibited the startle response to a 120 dB auditory stimulus in a graded fashion. Galantamine (depending on dose) improved PPI deficits in all three PPI disruption models, whereas donepezil ameliorated PPI deficits induced by scopolamine and apomorphine, but was not effective in the MK801 model. These results indicate that some AChEIs may have the potential to improve cognition in schizophrenia by improving auditory sensory gating.

Keywords

acetylcholine; acetylcholinesterase; cholinergic; cognition; memory; schizophrenia

INTRODUCTION

Acetylcholinesterase inhibitors (AChEIs) such as donepezil, rivastigmine, and galantamine are commonly used to treat the memory impairments associated with Alzheimer's Disease (AD). This therapeutic approach is based on several large clinical studies of AChEIs in which symptomatic improvements were observed in patients diagnosed with mild to moderate AD (Boada-Rovira et al., 2004; Mintzer and Kershaw, 2003; Raskind et al., 2000; Winblad et al., 2001). There is also increasing evidence that AChEIs may have a therapeutic role for the memory dysfunction associated with a variety of conditions beyond AD, particularly those illnesses that are characterized by presynaptic cholinergic deficits such as Parkinson's Disease,

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Dementia with Lewy bodies, and Down syndrome (for review see Gustavson and Cummings, 2003).

Interestingly, there is some evidence to suggest that cholinergic function is altered in schizophrenia (thus leading to the question of whether AChEIs might be of benefit in this illness). For example, significant correlations between reduced choline acetyltransferase (i.e., ChAT, the acetylcholine synthesizing enzyme) levels and impaired cognition in schizophrenia have been observed (reviewed, Powchik et al., 1998). Moreover, decreases in both low affinity (α_7) nicotinic acetylcholine receptors (nAChRs) in the hippocampus and high affinity ($\alpha_4\beta_2$) nAChRs in the hippocampus, cortex, striatum, and thalamus have been detected in postmortem brains of schizophrenics (reviewed, Friedman 2004). The number of M_1/M_4 muscarinic acetylcholine receptors (mAChRs) have also been found to be reduced relative to normal postmortem brains in several areas including the hippocampus (Crook et al., 2000), prefrontal cortex (Crook et al., 2001) and striatum (Dean et al., 1996). Likewise, single photon emission computed tomography (SPECT) in living, unmedicated schizophrenic patients revealed fewer mAChRs in frontal, temporal, and occipital cortex as well as in the striatum and thalamus compared to control subjects (Raedler et al., 2003).

The cholinergic alterations described above may have particular importance to certain features of schizophrenia such as sensory gating abnormalities which are believed to contribute to deficits in attention, cognitive impairment, and possibly hallucinations (Adler et al., 1998). The disruption of “prepulse inhibition” (PPI), a well characterized model for identifying sensory information-processing deficits, is in fact, clearly established in schizophrenia (reviewed, Braff et al., 2001). PPI is defined as the reduction in startle response produced by a low-intensity stimulus presented before a high-intensity, startle-producing stimulus (Graham et al., 1975). Further, PPI is known to be heavily influenced by the hippocampus, thalamus and striatum (reviewed, Swerdlow et al., 2001), i.e., brain regions identified as deficient in cholinergic receptors in schizophrenic patients (see above). The importance of nicotinic-cholinergic function in these brain regions (in particular, in the hippocampus) to PPI has been exemplified in recent clinical studies in which nicotine enhanced tactile PPI in both healthy subjects and schizophrenic patients. The correlational analysis between the enhancement of PPI and the change in neural activation after nicotine (detected by functional magnetic resonance imaging) identified the hippocampus as the primary structure for this modulatory effect of nicotine (Postma et al., 2006).

The measurement of PPI affords many advantages for clinical studies of schizophrenia as well as for the therapeutics of the illness. As summarized by Kumari and Sharma, 2002, impairments in PPI predict poor responses on the Ego Impairment Index-human experience scale, poor performance on the Wisconsin Card Sort Test, and elevated levels of distractibility. The fact that PPI is a cross-species phenomenon also allows for translation between animal experiments and clinical studies (Swerdlow et al., 1999). Accordingly, a number of animal models of PPI impairment have been developed which include neonatal ventral hippocampal lesion, maternal deprivation, isolation rearing, genetic, and pharmacological models, the later being commonly used in antipsychotic drug development studies (Geyer et al., 2001). Such pharmacological models have provided evidence that the neurotransmitters dopamine (Mansbach et al., 1988), glutamate (Mansbach and Geyer, 1989), serotonin (Sipes and Geyer, 1994), and acetylcholine (Jones and Shannon, 2000), are each likely to play an important role in normal sensory gating and PPI as well as disorders of these processes.

Given the established efficacy of AChEIs in the treatment of AD and a variety of animal studies in which cholinergic agonists such as nicotine and cotinine have been observed to enhance PPI (see Terry et al., 2005), we were interested to learn if AChEIs might have the potential to improve PPI. In this study, we compared two commonly used acetylcholinesterase inhibitors,

donepezil and galantamine, for ability to improve pharmacologically induced deficits in PPI in rodents using dopamine receptor agonism by apomorphine, NMDA receptor antagonism by MK801, or muscarinic acetylcholine receptor antagonism by scopolamine.

METHODS

Study subjects

One hundred and seventy male albino Wistar rats (2-3 months old) were obtained from Harlan Sprague-Dawley, Inc.) and housed in pairs in a temperature controlled room (25°C), maintained on a 12-hour light/dark cycle with free access to food (Teklad Rodent Diet 8604 pellets, Harlan, Madison, WI) and water. Fifty animals were used in experiments to evaluate the effects of the AChEI's alone on startle amplitude and PPI, 50 rats were used for the galantamine-PPI inhibitor experiments, 50 rats were used for the donepezil-PPI inhibitor experiments, and finally, 20 rats were used to confirm previous (unpublished) results which indicated a lack of significant effect of repeated testing (i.e., up to 4 total exposures to the PPI test) on startle amplitude and PPI. Thus, after habituation to the test apparatus and an initial trial of only startle and prepulse stimuli (described further below), the animals were given one full 60-trial PPI session to establish baseline startle response and PPI levels. After this session, the animals were matched for average startle amplitude (into groups of 8-10) and then assigned to one of the treatment combinations or vehicle-vehicle (see below). Specifically, the groups were assigned to receive one of the treatment combinations and tested a maximum of 3 times after the initial baseline session (when group assignments were made) over an additional 3 week period. Using a balanced crossover design, the AChEI doses and exposure to PPI antagonists were pseudorandomized to obviate any effects associated with the order of drug administration.

All procedures employed during this study were reviewed and approved by the Medical College of Georgia Institutional Animal Care and Use Committee and are consistent with AAALAC guidelines. Measures were taken to minimize pain or discomfort in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996. Significant efforts were also made to minimize the total number of animals used while maintaining statistically valid group numbers.

Drugs

All drugs were dissolved in vehicle (0.9% NaCl) and administered in a volume of 1.0 ml/kg. For the dose-effect studies in which the effects of the AChEIs alone on PPI were evaluated, galantamine (Galantamine hydrobromide, Janssen Pharmaceutica, Beerse, Belgium) or donepezil (A&A Pharmachem, Ottawa, Ontario Canada) was injected subcutaneously (s.c.) 30 min before testing followed by vehicle s.c., 10 min before testing. For the apomorphine and MK801 reversal studies, test subjects were administered vehicle or the AChEI s.c., 30 min before testing followed by either vehicle, apomorphine (Sigma A4393) 0.5 mg/kg, or MK-801 (Sigma M-107) 0.1 mg/kg s.c., 10 min before testing. For the scopolamine-reversal studies, scopolamine HBr (Sigma S1875) 0.33 mg/kg was administered 40 min before testing followed by either vehicle or AChEI 20 min before testing. The PPI methods and the compounds used to disrupt PPI (and their doses) were based on earlier studies (Mansbach et al., 1988; Mansbach and Geyer, 1989; Jones and Shannon, 2000b) and recent work in our laboratory (Terry et al., 2005). Galantamine was tested at doses of 0.3, 1.0, and 3.0 mg/kg while donepezil doses were 0.5, 1.0, and 2.0 mg/kg. These doses were based on data obtained in rats in which brain levels of the compounds and the degree of acetylcholinesterase inhibition were compared across a dose and time (Geerts et al., 2005) as well as recent neuropharmacological and behavioral studies in our laboratory (Hernandez et al., 2006).

Behavior testing

All animals were individually handled daily for several minutes for at least one week prior to experimentation. Tests were conducted in four standard startle chambers (San Diego Instruments, San Diego, CA) each consisting of a Plexiglas tube (diameter 8.2 cm, length 25 cm), placed in a sound-attenuated chamber. The tube is mounted on a plastic frame, under which a piezoelectric accelerometer is mounted which records and transduces the motion of the tube. Two days before PPI testing, the experimental subjects were each placed in one of the startle test chambers for a period of 20 minutes (without any startle stimuli) as an initial period of acclimation to the apparatus. One day before drug testing the animals were again placed in the test chamber and then exposed to a 5 min habituation period during which 70 dB background white noise was present. This period was followed by twelve startle stimuli and each prepulse level 3 times (see below). This procedure was conducted in order to reduce the highly variable responses to the initial exposures to the startle stimuli as well as to ensure that the prepulse stimuli (alone) had no significant effect on the startle response.

On the day of PPI testing, experimental subjects were transported to the startle chamber room and left undisturbed for at least 30 min. Afterwards, the rats were placed in the chamber and then allowed to habituate for a period of 1.0 min. After this period, the rats received 12 startle trials, 12 no-stimulus trials, and 12 trials of each of the prepulse/startle trials (see below) for a total of 60 trials. The intertrial interval ranged from 10 to 30 sec, and the total session lasted about 25-30 min. The startle trials consisted of single 120 dB white noise bursts lasting 20 ms. The PPI trials consisted of a prepulse (20 ms burst of white noise with intensities of 75, 80, or 85 dB) followed 100 ms later by a startle stimulus (120 dB, 20 ms white noise). During the no-stimulus trial, no startle noise was presented, but the movement of the rat was scored. This represented a control trial for detecting differences in overall activity. The different trial types were presented pseudo-randomly, each trial type was presented 12 times, and no two consecutive trials were identical. The resulting movement of the rat in the startle chamber was measured during 100 ms after startle stimulus onset (sampling frequency 1 kHz), rectified, amplified, and fed into a computer that calculated the maximal response over the 100-ms period. Basal startle amplitude was determined as the mean amplitude of the 12 startle trials. PPI was calculated according to the formula $100 - 100\% \times (PPx/P120)$, in which PPx is the mean of the 12 prepulse inhibition trials (i.e., for each individual prepulse intensity), and p120 is the basal startle amplitude. The average level of PPI was also calculated (mean of the responses to pp75, pp80, or pp85) and analyzed separately.

Statistical Analyses

All data were collated and entered into Microsoft Excel spreadsheets. The data were subsequently imported into SigmaStat version 2.03 for statistical analyses. A one or two-way ANOVA (with repeated measures when indicated) was used for all treatment comparisons and the Student-Newman-Keuls method was used for post hoc analyses.

RESULTS

Effects of Repeated PPI Testing

As indicated in the Methods, a series of experiments were conducted to ensure that repeated exposure to PPI testing (i.e., up to 4 total exposures) did not result in significant changes in startle amplitude or levels of PPI. A group of twenty rats were tested in an initial PPI session, then 10 subjects with similar startle amplitudes and PPI levels were tested once per week for 3 additional sessions (i.e., to mimic the drug study design). As indicated in Fig. 1A, there were highly significant differences in the responses to the various prepulse levels ($F_{(2,18)}=36.3$, $p<0.001$) as expected, however, there were no significant effects of the session (i.e., all p values were > 0.05) when the level of PPI or startle amplitude was analyzed (see Fig 1A-C).

Effects of the AChEI's Alone on Startle and PPI

In all of the PPI studies described below, there was a highly significant reduction in the startle response which was dependent upon the magnitude of the prepulse stimulus (i.e., prepulse level difference $p < 0.001$ in all studies—see the open bars in the A insets of Figs. 2-7). As indicated in Table 1, there were no significant (i.e. $p > 0.05$) effects of galantamine or donepezil on PPI across the doses evaluated nor was there a significant treatment $\times$ prepulse level interaction. Similar effects were obtained when the data were averaged across prepulse level (right hand column of Table 1). In addition, there were no significant effects of either donepezil or galantamine on the startle amplitude.

Effects of the AChEIs on Pharmacological Inhibitors of PPI

Galantamine

Attenuation of apomorphine As indicated in Fig. 2A, there were significant differences in responses to the various drug treatments (treatment effect, $F_{(4,42)} = 4.7$, $p = 0.003$; the effects of the prepulse levels, $F_{(2,8)} = 88.2$, $p < 0.001$), but the treatment $\times$ prepulse level interaction was not significant. Post hoc analyses indicated that apomorphine (0.5 mg/kg) significantly ($p < 0.05$) diminished PPI at all three prepulse levels when the effect was compared to the vehicle-associated response. Post hoc analyses further indicated that galantamine at the 3.0 mg/kg dose ameliorated the deficits in PPI produced by apomorphine at the 75, 80, and 85 dB prepulse levels. While the 1.0 mg/kg dose of galantamine also ameliorated the deficits induced by apomorphine on PPI at each prepulse level, the effects did not reach the required level of significance (i.e., $p > 0.05$). The positive effect of the 3.0 mg/kg dose of galantamine was also apparent when the data were averaged across the prepulse levels (see Fig. 2C). There were no significant effects of apomorphine or the galantamine - apomorphine combination on startle amplitude (Fig. 2B).

Attenuation of MK801 As indicated in Fig. 3A, there were significant differences in response to the various drug treatments (treatment effect $F_{(4,45)} = 4.4$, $p = 0.004$; the effects of the prepulse levels $F_{(2,8)} = 99.4$, $p < 0.001$), although the treatment $\times$ prepulse level interaction was not significant. Post hoc analyses indicated that MK801 (0.1 mg/kg) significantly ($p < 0.05$) diminished PPI (at all prepulse levels) when compared to the vehicle-associated response. Post hoc analysis further indicated that galantamine at a dose of 3.0 mg/kg significantly attenuated the deficits in PPI produced by MK801 at the 85 dB level. This positive effect of galantamine was also apparent when the data were averaged across the prepulse levels (see Fig. 3C). There were no significant effects of MK801 or the galantamine -MK801 combination on startle amplitude (Fig. 3B).

Attenuation of scopolamine As indicated in Fig. 4A, the treatment responses were significantly different (treatment effect $F_{(4,42)} = 4.1$, $p = 0.007$; as were the effects of the different prepulse levels $F_{(2,8)} = 114.8$, $p < 0.001$), although the treatment $\times$ prepulse level interaction was not significant. Post hoc analyses indicated that scopolamine significantly ($p < 0.05$) diminished PPI (at 75 and 80 dB levels) when compared to the vehicle-associated response. Post hoc analysis further indicated that galantamine at a dose of 1.0 mg/kg improved the deficits in PPI produced by scopolamine at these same two prepulse levels. These positive effects of galantamine were also apparent when the data were averaged across the prepulse levels (see Fig. 4C). There were no significant effects of scopolamine or the galantamine -scopolamine combination on startle amplitude (Fig. 4B).

Donepezil

Attenuation of apomorphine As shown in Fig. 5A, significant differences were also produced in the donepezil-apomorphine interaction study in response to the various drug treatments

(treatment effect, $F_{(4,42)}=6.4$, $p<0.001$; the effects of the prepulse levels were different, $F_{(2,8)}=61.6$, $p<0.001$), and the treatment $\times$ prepulse level interaction was significant, $F_{(88,146)}=2.1$, $p=0.043$. Post hoc analyses indicated that apomorphine significantly ($p<0.05$) diminished PPI (at 75 and 80 dB levels) when compared to the vehicle-associated response. Post hoc analysis indicated that donepezil 1.0 mg/kg significantly ($p<0.05$) improved deficits at these prepulse intensities. Post hoc analysis also confirmed the positive effects of 1.0 mg/kg donepezil when the data were averaged across the prepulse levels (Fig 5C). In addition, there were no significant effects of apomorphine or the donepezil-apomorphine combination on startle amplitude (Fig. 5B).

Attenuation of MK801 As exhibited in Fig. 6A, significant differences were also observed in the donepezil-MK801 interaction study in response to the various drug treatments (treatment effect, $F_{(4,44)}=2.9$, $p=0.031$; the effects of the prepulse levels, $F_{(2,8)}=98.5$, $p<0.001$), and the treatment $\times$ prepulse level interaction was significant, $F_{(88,146)}=4.6$, $p<0.001$. Post hoc analyses indicated that MK801 significantly ($p<0.05$) diminished PPI (at all prepulse levels) when compared to the vehicle-associated response. While there were some trends toward improvements of the MK801-related deficits by donepezil (e.g., the 2.0 mg/kg dose at 85 dB prepulse level) such improvements did not reach significance (i.e., all p values were >0.05). Similarly, there were no significant effects of donepezil on the MK801-associated response when the data were averaged across the prepulse levels (Fig 6C). Further, there were no significant effects of MK801 or the donepezil-MK801 combination on startle amplitude (Fig. 6B).

Attenuation of scopolamine Fig 7A shows that significant differences were produced in the donepezil-scopolamine interaction study in response to the various drug treatments (treatment effect, $F_{(4,40)}=2.8$, $p<0.038$; the effects of the prepulse levels were different, $F_{(2,8)}=80.8$, $p<0.001$), although the treatment $\times$ prepulse level interaction was not significant. Post hoc analyses indicated that scopolamine significantly ($p<0.05$) diminished PPI at the 80 dB prepulse level when the effect was compared to the vehicle-associated response. Post hoc analyses further indicated that donepezil at the 1.0 mg/kg dose improved the deficits in PPI produced by scopolamine at this prepulse level. The positive effect of the 1.0 mg/kg dose of donepezil was also apparent when the data were averaged across the prepulse levels (see Fig. 7C). Finally, there were no significant effects of scopolamine or the donepezil-scopolamine combination on startle amplitude (Fig. 7B).

DISCUSSION

There were 3 main findings in this study, 1) under vehicle conditions there were no significant effects of repeated exposures to the PPI test method on startle amplitude or PPI in rats for up to 3 sessions (i.e., after the initial test session to establish baselines), 2) neither galantamine nor donepezil had any significant effect on startle amplitude or PPI on their own, 3) galantamine (depending on dose) improved PPI deficits in all three pharmacologic models of PPI impairment, whereas donepezil ameliorated PPI deficits induced by scopolamine and apomorphine, but was not effective in the MK801 model. The lack of benefit of donepezil in the MK801 (PPI) model contrasts with behavioral studies in mice (Csernansky et al., 2005) where donepezil attenuated MK801-induced deficits in fear conditioning as well as spatial and reversal learning better than galantamine. The basis of the differential effects of the compounds observed in our studies and the one cited above is unclear, although there are some differences in the pharmacology of these compounds (i.e., other than that related to AChEI activity) that may be of importance. For example, in culture studies, galantamine, has been observed to potentiate NMDA currents in rat cortical multipolar neurons (Moriguchi et al., 2005). In contrast, donepezil, potentiated NMDA receptors in both bipolar and multipolar neurons, but its effects on multipolar neurons were biphasic. Specifically, donepezil suppressed NMDA-

induced currents at moderate concentrations and potentiated them only at concentrations likely too high to be therapeutically relevant.

In contrast to donepezil, galantamine also functions as a positive allosteric modulator of nAChRs *in vitro* which results in an amplification of the action of the acetylcholine (Maelicke et al., 2001). These nAChR effects of galantamine are interesting in light of reports that cigarette smoking temporarily normalizes sensorimotor gating deficits in schizophrenics (Adler et al., 1993; Kumari et al., 2001), and animal data indicating that chronic nicotine treatment reduced attentional impairments induced by the antipsychotics, haloperidol (Rezvani and Levin, 2004), risperidone, and clozapine (Rezvani et al., 2006). Thus, given the emerging importance of nAChR function in schizophrenia, and the known positive effects of nicotinic agonists on schizophrenic symptoms, the allosteric actions of galantamine at nAChRs could be an important pharmacological advantage.

The observation that both AChEIs improved scopolamine-related decreases in PPI were not particularly surprising since the compounds are well documented to increase synaptic levels of acetylcholine, an effect that would presumably overcome the scopolamine antagonism at muscarinic receptors as well as increase tone at unblocked nicotinic receptors. The experiments were conducted, however, to confirm that this pharmacological action (i.e., improved cholinergic function) indeed likely contributed to the effects of these compounds on PPI. Other animal data that support such a premise are evident in a recent study in which PPI deficits induced by immunolesions of cholinergic neurons of the nucleus basalis were reversed by the AChEI, rivastigmine (Ballmaier et al., 2002). Additional data to support the role of muscarinic receptors in PPI (and that these receptors could serve as targets for drug development in schizophrenia) have been reported in a recent study in which, xanomeline, an M₁/M₄ AChR agonist (Jones et al., 2005; Stanhope et al., 2001), normalized apomorphine-reduced PPI levels.

The data described in this report thus support the hypothesis that AChEIs might have the potential to serve as therapeutic options for schizophrenia by improving PPI and cognitive function. To date, however, the data collected in the relatively small number of clinical studies that have been designed to evaluate the potential cognitive benefits of AChEIs in schizophrenia have been equivocal. For example, the beneficial effects of donepezil or rivastigmine on cognition in schizophrenics as add-on treatments to antipsychotics observed in small preliminary investigations, open-label studies and case reports (e.g., Buchanan et al., 2003; Stryjer et al., 2003; Lenzi et al., 2003) were not confirmed in larger randomized, double-blind, and placebo controlled studies (see Friedman et al., 2002; Freudenreich et al., 2005; Sharma et al., 2006). In the case of galantamine, there are also several small studies that indicate a potential benefit to schizophrenic patients including a recent randomized, double-blind clinical trial (N=8) where the AChEI improved short-term memory and attention in schizophrenic or schizoaffective patients who were stabilized on risperidone (Schubert et al., 2006). While such data are encouraging, much larger studies will be required to verify the validity of this approach as a reliable therapeutic intervention in schizophrenia.

As in the case of schizophrenia, there are several small clinical studies that would support the use of AChEIs as adjunctive therapy in other psychiatric and neurological disorders where PPI deficits have been reported. For example, donepezil and rivastigmine have been observed to improve several autistic behaviors in children (Hardan and Handen, 2002; Chez et al., 2004), while in autistic adults, adjunctive galantamine therapy enhanced language and communication skills (Hertzman, 2003). In addition, rivastigmine and galantamine have been observed to improve cognitive function as well as hallucinations in Parkinson's disease patients (Bullock and Cameron, 2002; Aarsland et al., 2003) and further, rivastigmine has been reported to ameliorate cognitive deficits and slow motor deterioration in patients with Huntington's Disease (de Tommaso et al., 2004).

In summary, the results of this rodent study indicate that the clinically used AChEIs, galantamine and donepezil, have the ability to improve auditory sensory gating in established pharmacologic models of impaired PPI. These data combined with the positive clinical data described above suggest that efforts to increase cholinergic activity (i.e., by cholinesterase inhibitors or other means) in the brain warrant further investigation as potential therapeutic options for schizophrenia and other conditions where PPI is disrupted.

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Fig 1.

Effects of repeated exposures to the PPI testing method in rats. **(A)** Level of prepulse inhibition associated with three prepulse intensities (75, 80, and 85 dB). **(B)** Startle amplitude. **(C)** Level of prepulse inhibition averaged across prepulse level. Bars represent mean $\pm$ S.E.M. for each session (N=10).

Fig 2.

(A) Effects of apomorphine (0.5 mg/kg) and several doses of galantamine on apomorphine-induced deficits in prepulse inhibition in rats associated with three prepulse intensities (75, 80, and 85 dB). (B) Effects of apomorphine and galantamine combined with apomorphine on startle amplitude. (C) Effects of apomorphine (0.5 mg/kg) and several doses of galantamine on apomorphine-induced deficits in prepulse inhibition averaged across prepulse level. Bars represent mean $\pm$ S.E.M. for each treatment (N=8-10). VEH = vehicle; GAL = galantamine; APO = apomorphine. * = significantly different ($p < 0.05$) than the vehicle associated response. + = significantly different ($p < 0.05$) than the apomorphine-associated response.

Fig 3.

(A) Effects of MK801 (0.1 mg/kg) and several doses of galantamine on MK-801-induced deficits in prepulse inhibition in rats associated with three prepulse intensities (75, 80, and 85 dB). (B) Effects of MK801 and galantamine combined with MK801 on startle amplitude. (C) Effects of galantamine on MK801-induced deficits in prepulse inhibition averaged across prepulse level. Bars represent mean $\pm$ S.E.M. for each treatment (N=10). VEH = vehicle; GAL = galantamine. * = significantly different ($p < 0.05$) than the vehicle associated response. + = significantly different ($p < 0.05$) than the MK801-associated response.

Fig 4.

(A) Effects of scopolamine (0.33 mg/kg) and several doses of galantamine on scopolamine-induced deficits in prepulse inhibition in rats associated with three prepulse intensities (75, 80, and 85 dB). (B) Effects of scopolamine and galantamine combined with scopolamine on startle amplitude. (C) Effects of galantamine on scopolamine-induced deficits in prepulse inhibition across prepulse level. Bars represent mean $\pm$ S.E.M. for each treatment (N=8-10). VEH = vehicle; SCOP = scopolamine; DON= donepezil. * = significantly different ($p < 0.05$) than the vehicle associated response. + = significantly different ($p < 0.05$) than the scopolamine-associated response.

Fig 5.

(A) Effects of apomorphine (0.5 mg/kg) and several doses of donepezil on apomorphine-induced deficits in prepulse inhibition in rats associated with three prepulse intensities (75, 80, and 85 dB). (B) Effects of apomorphine and donepezil combined with apomorphine on startle amplitude. (C) Effects of apomorphine (0.5 mg/kg) and several doses of donepezil on apomorphine-induced deficits in prepulse inhibition averaged across prepulse level. Bars represent mean $\pm$ S.E.M. for each treatment (N=8-10). VEH = vehicle; DON = donepezil; APO = apomorphine. * = significantly different ($p < 0.05$) than the vehicle associated response. + = significantly different ($p < 0.05$) than the apomorphine-associated response.

Fig 6.

(A) Effects of MK801 (0.1 mg/kg) and several doses of donepezil on MK-801-induced deficits in prepulse inhibition in rats associated with three prepulse intensities (75, 80, and 85 dB).

(B) Effects of MK801 and donepezil combined with MK801 on startle amplitude. (C) Effects of donepezil on MK801-induced deficits in prepulse inhibition averaged across prepulse level. Bars represent mean $\pm$ S.E.M. for each treatment (N=9-10). VEH = vehicle; DON = donepezil.

* = significantly different ($p < 0.05$) than the vehicle associated response. + = significantly different ($p < 0.05$) than the MK801-associated response.

Fig 7.

(A) Effects of scopolamine (0.33 mg/kg) and several doses of donepezil on scopolamine-induced deficits in prepulse inhibition in rats associated with three prepulse intensities (75, 80, and 85 dB). (B) Effects of scopolamine and donepezil combined with scopolamine on startle amplitude. (C) Effects of donepezil on scopolamine-induced deficits in prepulse inhibition across prepulse level. Bars represent mean $\pm$ S.E.M. for each treatment (N=8-10). VEH = vehicle; SCOP = scopolamine; DON= donepezil. * = significantly different ($p < 0.05$) than the vehicle associated response. + = significantly different ($p < 0.05$) than the scopolamine-associated response.

Table 1

AChEI Effects on Startle Response and PPI

Group	Startle (AU)	Nulstim	% PPI $\pm$ SEM			Mean
			75 dB	80 dB	85 dB	
VEH	776.1 $\pm$ 36.8	16.7 $\pm$ 2.4	51.3 $\pm$ 3.2	64.0 $\pm$ 3.8	81.2 $\pm$ 2.4	65.5 $\pm$ 2.4
0.5 DON	811.7 $\pm$ 258.6	21.2 $\pm$ 3.7	56.0 $\pm$ 8.7	66.2 $\pm$ 6.7	78.5 $\pm$ 4.6	66.9 $\pm$ 6.4
1.0 DON	489.5 $\pm$ 164.0	24.9 $\pm$ 4.1	57.0 $\pm$ 6.5	69.0 $\pm$ 5.5	75.8 $\pm$ 5.5	67.3 $\pm$ 5.2
2.0 DON	623.1 $\pm$ 142.0	13.0 $\pm$ 2.8	63.2 $\pm$ 3.0	70.8 $\pm$ 4.0	83.4 $\pm$ 3.1	72.4 $\pm$ 3.0
0.3 GAL	608.2 $\pm$ 93.8	17.7 $\pm$ 1.9	44.6 $\pm$ 6.8	61.7 $\pm$ 5.2	68.0 $\pm$ 6.1	58.1 $\pm$ 6.2
1.0 GAL	760.7 $\pm$ 221.7	21.3 $\pm$ 3.1	57.2 $\pm$ 5.8	69.6 $\pm$ 5.3	76.6 $\pm$ 4.4	67.8 $\pm$ 1.6
3.0 GAL	582.5 $\pm$ 204.3	15.2 $\pm$ 2.6	49.9 $\pm$ 8.7	60.2 $\pm$ 6.3	71.0 $\pm$ 5.7	59.6 $\pm$ 6.8