Neuropsychopharmacology (2006) 31, 2150–2161

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Disruption of Prepulse Inhibition after Stimulation of Central but not Peripheral α-1 Adrenergic Receptors

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Prepulse inhibition (PPI) refers to the attenuation of startle when a weak prestimulus precedes the startling stimulus. PPI is deficient in several psychiatric illnesses involving poor sensorimotor gating. Previous studies indicate that α1 adrenergic receptors regulate PPI, yet the extent to which these effects are mediated by central *vs* peripheral receptors is unclear. The present studies compared the effects of intracerebroventricular (ICV) *vs* intraperitoneal (IP) delivery of several α1 receptor agonists on PPI. Male Sprague–Dawley rats received either cirazoline (0, 10, 25, 50 μg/5 μl), methoxamine (0, 30, 100 μg/5 μl), or phenylephrine (0, 3, 10, 30 μg/5 μl) ICV immediately before testing. Separate groups received either cirazoline (0, 0.25, 0.50, 0.75 mg/kg), methoxamine (0, 2, 5, 10 mg/kg), or phenylephrine (0, 0.1, 2.0 mg/kg) IP 5 min before testing. PPI, baseline startle responses, and piloerection, an index of autonomic arousal, were measured. Cirazoline disrupted PPI; effective ICV doses were approximately six times lower than effective IP doses. Methoxamine disrupted PPI after ICV infusion but failed to affect PPI with IP doses that were up to 30-fold higher than the effective ICV dose. Phenylephrine disrupted PPI with ICV administration, but did not alter PPI after IP injection of even a 20-fold higher dose. None of the ICV treatments altered baseline startle magnitude, but phenylephrine and methoxamine lowered startle after administration of high systemic doses. Piloerection was induced by cirazoline via either route of administration, and by IP methoxamine and phenylephrine, but not by ICV infusion of methoxamine or phenylephrine. These findings indicate that α1 receptor-mediated PPI disruption occurs exclusively through stimulation of central receptors and is dissociable from alterations in baseline startle or autonomic effects.
Neuropsychopharmacology (2006) **31,** 2150–2161. doi:10.1038/sj.npp.1300989; published online 11 January 2006

Keywords: prepulse inhibition; startle; norepinephrine; noradrenaline; sensorimotor gating; schizophrenia

INTRODUCTION

Prepulse inhibition (PPI) is an operational measure of sensorimotor gating, a process by which an organism can filter the flow of information from its internal and external environments (Geyer *et al*, 1990). PPI refers to the normal diminution of the startle response when the startling stimulus is preceded immediately by a weak intensity prepulse, and is deficient in a number of psychiatric illnesses that involve disturbed sensorimotor gating, including schizophrenia (Braff *et al*, 1978; Hoffman and Ison, 1980; Ison and Hoffman, 1983). Sensorimotor gating, as indexed by PPI, represents an important form of preattentional information processing that is critical for the maintenance of selective attention and normal cognitive functioning (Braff and Light, 2004). A breakdown in PPI can thus have devastating effects, contributing to the sensory inundation and cognitive fragmentation that are often seen in disorders such as schizophrenia (Braff *et al*, 2001; McGhie and Chapman, 1961).

Despite the large number of studies on the neurotransmitter and neuroanatomical substrates of PPI (Geyer *et al*, 2001; Swerdlow *et al*, 2001), relatively little is known about the role of the norepinephrine (NE) system in regulating sensorimotor gating. This paucity is surprising, given the prominent role of NE in processes relevant to attention and cognitive functioning. A number of psychiatric illnesses with manifested dysfunction in attentional mechanisms are hypothesized to involve pathology of the NE system (Aston-Jones *et al*, 1999). PPI deficits can be seen in many of these conditions including attention-deficit-hyperactivity disorder (ADHD), schizophrenia, and post-traumatic stress disorder (PTSD); interestingly, with ADHD, this PPI disruption is seen only with attended-to prepulses (Braff *et al*, 2001; Castellanos *et al*, 1996; Grillon *et al*, 1996; Hawk *et al*, 2003; Ornitz *et al*, 1992). Thus, clarifying the nature of PPI modulation by NE may further our understanding of

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Received 17 May 2005; revised 3 October 2005; accepted 7 October 2005
Online publication: 28 October 2005 at http://www.acnp.org/citations/Npp102805050329/default.pdf

how this system regulates functions that are relevant to the information processing-related deficits observed in these illnesses.

Increased NE transmission has long been known to enhance the magnitude of the involuntary startle response (Astrachan *et al*, 1983; Kehne and Davis, 1985). In recent years, the potential clinical importance of NE regulation of PPI has been underscored by the finding that prazosin, an α1 adrenergic receptor antagonist, recapitulates the behavioral effects of atypical but not traditional antipsychotics on PPI by preventing PPI deficits induced by the psychotomimetics phencyclidine (PCP) and dizocilpine (Bakshi and Geyer, 1997, 1999). Accordingly, systemic administration of the α1 noradrenergic receptor agonist cirazoline disrupts PPI with a pharmacological profile identical to that of PCP (Carasso *et al*, 1998; Shilling *et al*, 2004; Varty *et al*, 1999). Thus, stimulation of adrenergic α1 receptors may represent an important mechanism through which the NE system regulates PPI.

One problem with these previous studies is that the α1 compounds were administered systemically, which raises the possibility that α1 receptor modulation of PPI might occur though the periphery rather than the central nervous system (CNS). Moreover, because α1 adrenergic receptor ligands significantly alter sympathetic nervous system activity, it is possible that PPI deficits induced by α1 agonists such as cirazoline are secondary to the sympathomimetic effects of these drugs (Guimaraes and Moura, 2001). Finally, while cirazoline is a potent agonist for the α1 receptor, it also has a high affinity for nonadrenergic imidazoline-binding sites (Wikberg and Uhlen, 1990), so the extent to which cirazoline-induced PPI deficits are mediated specifically by α1 receptors is unclear.

The present studies sought to resolve these questions regarding α1 receptor mediation of PPI. First, to test the hypothesis that CNS rather than peripheral receptors mediate PPI, the effects of central *vs* systemic administration of α1 receptor agonists with low blood–brain barrier permeability were compared. Second, to evaluate if α1 agonist-induced PPI deficits were associated with increased sympathetic tone, the concomitant effects of these drugs on piloerection, an index of autonomic sympathetic activity, were measured. Finally, to determine whether stimulation of imidazoline receptors contributes to cirazoline-induced PPI disruptions, the effects of cirazoline were compared to those of two highly selective α1 agonists with negligible affinity for imidazoline sites.

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats (Harlan Laboratories, Madison, WI and San Diego, CA) weighing 300–400 g were used in the present studies. Rats were housed in clear polycarbonate cages (two rats per cage) in a light- and temperature-controlled vivarium. Rats were maintained under a 12 h light/dark cycle (lights on at 0700 and off at 1900). Food and water were available to the rats *ad libitum*. All testing occurred between 0100 and 1500. Upon arrival, rats were handled daily by the experimenter. All facilities and procedures were in accordance with the guidelines regarding animal use and care put forth by the National Institutes of Health of the United States, and were supervised and approved by the Institutional Animal Care and Use Committee of the University of Wisconsin.

Surgery

Rats used for the intracerebroventricular (ICV) infusion studies (weighing 300–320 g at the time of surgery) were anesthetized with an intraperitoneal (IP) injection of xylazine/ketamine mixture (80 mg ketamine and 12 mg xylazine per ml of the mixture; 1 ml/kg given; Phoenix Scientific, St Joseph, MO), and then secured in a stereotaxic frame (Kopf Instruments, Tujunga, CA). Stainless-steel cannulae (23 gauge, Small Parts Inc., Miami Lakes, FL) were implanted and affixed to the skull with dental cement (Lang Dental Mfg Co, Wheeling, IL) and anchoring skull screws (Plastics One, Roanoke, VA) and were aimed unilaterally at the lateral ventricle using the coordinates described in the atlas of Paxinos and Watson (1998). Final coordinates were AP: −1.0 mm from bregma, ML: + 1.4 mm or −1.4 mm from midline (the laterality of the lateral-medial coordinate was alternated between rats), DV: −2.1 mm from skull surface. Wire stylets were placed in the cannulae to prevent blockage. After surgery, rats were given a recovery period of a week before testing (with daily health checks and handling).

Drugs

All drugs (cirazoline, methoxamine hydrochloride, phenylephrine hydrochloride, prazosin) were obtained from Sigma (St Louis, MO). All drugs except prazosin were dissolved in sterile isotonic (0.9%) saline; prazosin was dissolved with sonication in a vehicle solution of 1% dimethylsulfoxide in isotonic saline. Doses were calculated as salts, and the injection volume for systemic administration was 1 ml/kg; for all ICV experiments, the infusion volume was 5 μl.

Microinfusion Procedure

For ICV infusions, rats were wrapped loosely in a cotton dishtowel while stylets were removed and placed into 70% ethanol. The cannula was cleaned with a dental broach (Henry Schein, Melville, NY) and a stainless-steel injector (30 gauge, Small Parts Inc., Miami Lakes, FL) was lowered so that it extended 1.5 mm past the tip of the cannula. Thus, the final DV coordinate for the lateral ventricle was 3.6 mm below the skull surface. The injector was attached with polyethylene tubing (PE-10, Becton Dickinson and Co., Sparks, MD) to a 10-μl glass Hamilton syringe (Hamilton Co., Reno, NV). The Hamilton syringe was used to manually administer the infusate over approximately 2 s. The injector remained in place for an additional minute to allow for spreading of the drug through the ventricles before the injector was removed and the stylet was reinserted into the cannula.

Startle Chambers

All testing occurred within startle chambers obtained from San Diego Instruments (San Diego, CA). Each of the startle

chambers contained a nonrestrictive cylinder (made of Plexiglas) resting inside a ventilated and illuminated sound-attenuating cabinet. A high-frequency loudspeaker inside the chamber produced both a continuous background noise of 65 dB and the various acoustic stimuli. As described previously (Mansbach *et al*, 1988), the whole-body startle response of the animal caused vibrations of the Plexiglas cylinder, which were then converted into analog signals by a piezoelectric unit attached to the platform. These signals were digitized and stored by a microcomputer and interface unit. Monthly calibrations were performed on the chambers to ensure accuracy of the sound levels and measurements. Sound levels were measured using the dB(A) scale.

Figure 1 Photograph of criterion for piloerection rating. Left panel shows a representative rat not displaying piloerection, and the right panel shows a representative rat with piloerection. Rats had to exhibit at minimum the level of fur erectness seen in the right panel in order to be classified as displaying piloerection by the experimenter, who was blind to the drug treatments.

Startle and PPI Testing

All startle sessions (baseline and test session) employed a continuous background noise of 65 dB that was presented alone for 5 min at the beginning of the session, and remained on throughout the entire session. At 2–3 days prior to the first test day, all rats underwent a brief (baseline) startle session to familiarize them with the testing procedure and to create matched treatment groups based on baseline startle responses (for Experiments 1b, 3a, 3b, and 4). Immediately prior to the baseline startle session, rats that were to receive ICV infusions during the test session were given sham infusions (during which injectors were lowered but no infusion was given). The baseline startle session contained a total of 15 trials presented in a pseudo-random order (ten 120-dB Pulse−Alone trials and five Prepulse + Pulse trials with a 77-dB prepulse and a 120-dB pulse; see below for trial definitions). The test session used in the experiments consisted of presentation of (in a pseudo-random order) 120-dB Pulse−Alone trials (a 40-ms, 120-dB broadband burst), Prepulse + Pulse trials (20-ms noises that were 3, 6, or 12 dB above the background noise and were presented 100 ms before the onset of the 120-dB pulse) and No Stimulus trials (only the background noise). The test session contained at total of 60 trials (10 each of the 3-, 6-, and 12-dB Prepulse + Pulse trials, 22 Pulse−Alone trials and eight No Stimulus trials). In addition, four Pulse−Alone trials were presented at the beginning and the end of the session; these trials were excluded from the analysis of startle and percent PPI but were used to achieve stable startle responses during the test session since steep habituation to the pulse is known to occur within the first few startle presentations (Geyer *et al*, 1990).

Experimental Protocol

Seven studies were conducted using separate groups of experimentally naïve rats. In each experiment, all rats were rated for the presence or absence of piloerection by an experimenter blind to the experimental conditions upon removal of rats from the startle chambers (approximately 30 min after pharmacological treatment). Figure 1 depicts a representative example of a control rat (no piloerection), and a cirazoline-treated rat exhibiting piloerection; a rat had to display at least the level of fur erectness shown in the right panel of Figure 1 to receive a positive piloerection score.

Experiment 1a examined the effects of central administration of the α1 agonist, cirazoline, on PPI. Rats ($N=9$) were given an ICV infusion of one dose of cirazoline (0, 10, 25, or 50 μg/5 μl) immediately prior to testing in the startle chambers. The doses were administered in a counterbalanced order, using a within-subjects design with at least one day separating consecutive testing days so that each rat received all doses over 4 test days. Experiment 1b examined the effects of systemically administered cirazoline on PPI. Rats ($N=6$–9/dose) were treated with an IP injection of cirazoline (saline, 0.25, 0.5, or 0.75 mg/kg) 5 min prior to testing in the startle chambers. The drug treatments were administered in a between-subjects design.

Experiment 2a examined the effects of central administration of a more selective α1 agonist methoxamine, which lacks imidazoline affinity and does not readily cross the blood–brain barrier (Holz *et al*, 1982). Rats ($N=12$) were given an ICV infusion of methoxamine (0, 30, or 100 μg/5 μl) immediately prior to testing in the startle chambers. The methoxamine doses were administered in a counterbalanced, within-subjects design with at least 1 day separating consecutive test days. Experiment 2b examined the effects of systemic administration of methoxamine on PPI. Animals ($N=6$) were treated with an IP injection of methoxamine (0, 2, 5, 10 mg/kg) 5 min prior to testing in the startle chambers. The drug treatments were administered in a counterbalanced, within-subjects design with at least 1 day separating the testing days.

Experiment 3a assessed the effects of central administration of phenylephrine, another nonimidazoline α1 agonist with low permeability into the brain, on PPI (Guo *et al*, 1991; Holz *et al*, 1982). Rats ($N=6$–7/dose) were treated with an ICV infusion of one dose of phenylephrine (0, 3, 10, or 30 μg/5 μl) and immediately afterwards tested in the startle chambers using a between-subjects design. In Experiment 3b, the effects of systemic phenylephrine on PPI were evaluated. Rats ($N=6$/group) were given an IP injection of either phenylephrine (0.1 mg/kg) or saline 5 min before being tested in the startle chambers. An additional group of rats ($N=7$) was given an IP injection of either phenylephrine (2.0 mg/kg) or saline 5 min before being tested in the startle chambers. These experiments employed a between-subjects design.

In the final experiment, Experiment 4, the effects of antagonism of α1 receptors on α1 agonist-induced PPI deficits was evaluated. Rats ($N=5$/group) were given an IP

injection of the α1 antagonist prazosin (1 mg/kg) or vehicle 25 min prior to an IP injection of cirazoline (0.5 mg/kg) or saline (in a 2 × 2 between-subjects design). Rats were tested for PPI 5 min following the second IP injection. Note that this dose of prazosin was chosen on the basis of its previously demonstrated ability to block cirazoline- or PCP-induced PPI deficits (Bakshi and Geyer, 1997; Carasso *et al*, 1998).

Upon completion of the ICV experiments, the placement of the cannula in the lateral ventricle was confirmed for each rat. Rats were given an overdose of pentobarbital (Abbot laboratories, North Chicago, IL) and given an infusion of 5 μl of Chicago Sky Blue Dye (Sigma, St Louis, MO) using the same procedure outlined above for infusion of the α1 adrenergic agonists. After infusion of the dye, rats were decapitated and brains were sliced into 1-mm sections. Only rats for which blue dye was observed in the third and fourth ventricles were considered to have accurate cannula placements in the lateral ventricle.

Data Analysis

The startle response to the onset of the 120-dB burst was recorded for 100 ms for each Pulse−Alone and Prepulse + Pulse trial. Two measurements (startle magnitude and PPI) were calculated from these values for each rat for each of the different treatment conditions. Startle magnitude was calculated by taking the average of the startle responses to the Pulse−Alone trials. PPI was calculated as a percent score for each Prepulse + Pulse trial type: %PPI = 100−(((startle response for Prepulse + Pulse trial)/(startle response for Pulse−Alone trial)) × 100). Startle magnitude data were analyzed with one-factor ANOVAs with treatment as either a between-subjects (Experiments 1b, 3a, 3b, 4) or a within-subjects (Experiments 1a, 2a, 2b) factor. PPI data were analyzed with two-factor repeated-measures ANOVAs with treatment as either a between-subjects (Experiments 1b, 3a, 3b, 4) or a within-subjects (Experiments 1a, 2a, 2b) factor and prepulse intensity as a repeated measure. Piloerection data were analyzed using Cochran's *Q*-tests to compare the frequency of piloerection observed in the rats for each drug condition (number of rats exhibiting piloerection per total number of rats in that treatment condition). *Post hoc* analyses were done using Tukey's *t*-tests. The α level for significance was set at 0.05. Note that for all experiments in which drug treatment was a within-subjects variable, treatment day was initially included as an additional factor in the ANOVA; however, as no main effects of treatment day or interactions between treatment day and any other factor were observed (indicating that there were no carry-over effects from prior α1 agonist administration), only the results of the 1- and 2-factor ANOVAs described above are presented (for the sake of brevity). Finally, startle responses to the first four (block 1) and last four (block 2) 120-dB Pulse−Alone trials (omitted from the calculation of startle magnitude and PPI) were analyzed with separate 2-factor ANOVAs (block and drug dose as factors) for each dose–response Experiment, and a 3-factor ANOVA (block, pretreatment, treatment as factors) for experiment 4 in order to evaluate the effects of the drug treatments on short-term startle habituation.

RESULTS

In every experiment, there was a significant main effect of prepulse intensity, indicating that percent PPI increased with increasing prepulse intensity. This effect is a well-known parametric feature of PPI (Geyer *et al*, 2001). For the sake of brevity, these main effects are not reported below for each individual experiment. Additionally, there were no significant effects on startle habituation in any experiment; for the sake of brevity, these null findings are not reiterated below.

Effects of Cirazoline on PPI

ICV cirazoline. The results from Experiment 1a are illustrated in Figure 2a. Centrally administered cirazoline significantly disrupted PPI, as shown by the main effect of treatment on PPI ($F(3,24) = 6.4$, $P < 0.002$). In addition, there was a significant interaction between treatment and prepulse level ($F(6,48) = 3.4$, $P < 0.007$). Subsequent *post hoc* tests revealed a significant reduction of PPI by the 25-μg dose of cirazoline at the 3-dB ($P < 0.05$) prepulse level and a decrease at the 6-dB and 12-dB prepulse levels by the 50-μg dose ($P < 0.01$), compared to the vehicle treatment.

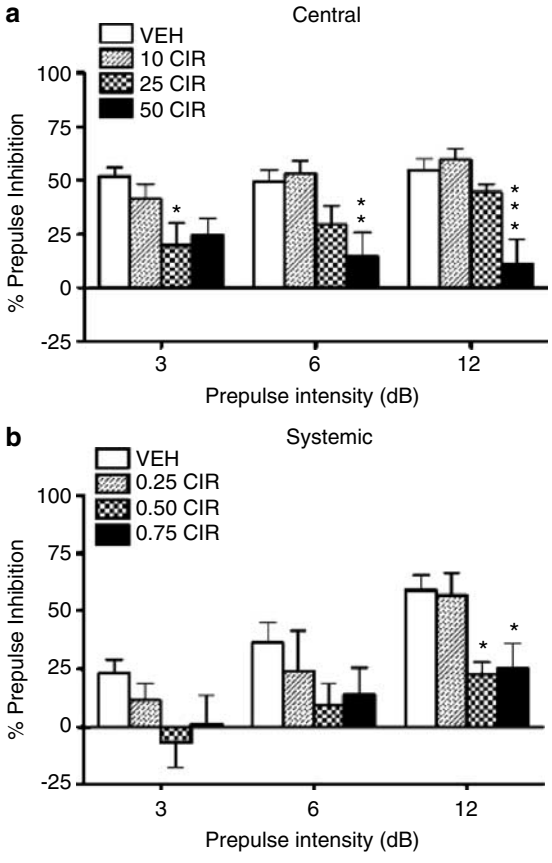

Figure 2 (a and b) Effects of central (a) and systemic (b) administration of the α1 agonist cirazoline on PPI. VEH = vehicle; CIR = cirazoline. Prepulse intensity = decibels above background noise. Values are shown as mean ± SEM. Central doses are in μg/5 μl and systemic doses are in mg/kg. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, relative to respective vehicle conditions.

IP cirazoline. The results from Experiment 1b are shown in Figure 2b. Similar to ICV cirazoline, systemically administered cirazoline disrupted PPI as demonstrated by the main effect of treatment on PPI ($F(3,23) = 3.5$, $P < 0.03$); this result replicates our previous report of disrupted PPI with systemic cirazoline administration (Carasso *et al*, 1998). *Post hoc* tests revealed that the 0.5 mg/kg dose ($P < 0.05$) and the 0.75 mg/kg ($P < 0.05$) dose significantly lowered PPI compared to vehicle treatment at the 12-dB prepulse level. It is important to note that the lowest dose of IP cirazoline that disrupted PPI was 0.5 mg/kg while the lowest dose of ICV cirazoline that disrupted PPI was 25 μg. Thus, the central dose of cirazoline that disrupted PPI was six-fold lower than the minimum effective systemic dose (for rats weighing approximately 300 g, as those in the present study).

Effects of Methoxamine on PPI

ICV methoxamine. Experiment 2a sought to compare the effects on PPI of methoxamine, an α1 agonist that lacks imidazoline-binding and does not readily penetrate the brain when given systemically (Holz *et al*, 1982). The results from Experiment 2a are illustrated in Figure 3a. Centrally administered methoxamine dose dependently disrupted PPI, as shown by the main effect of treatment on PPI ($F(2,24) = 5.7$, $P < 0.01$). *Post hoc* tests revealed a significant disruption in PPI by the 100-μg dose at the 12-dB prepulse level ($P < 0.05$).

IP methoxamine. The results from Experiment 2b are illustrated in Figure 3b. In contrast to ICV methoxamine, there was no effect of systemically administered methoxamine on PPI ($F(3,16) = 0.5$, NS). Therefore, the highest IP dose of methoxamine, 10 mg/kg, failed to disrupt PPI while a 30-fold lower dose, 100 μg, disrupted PPI when given centrally.

Effects of Phenylephrine on PPI

ICV phenylephrine. The results from Experiment 3a are shown in Figure 4a. Similar to methoxamine, central administration of the nonimidazoline α1 agonist phenylephrine disrupted PPI, as shown by the main effect of treatment on PPI ($F(2,18) = 4.9$, $P < 0.02$). *Post hoc* tests revealed a significant disruption by the 30-μg dose at the 12-dB prepulse level ($P < 0.01$).

IP phenylephrine. The results from Experiment 3b are illustrated in Figure 4b. In contrast to ICV phenylephrine, there was no effect of systemically administered phenylephrine on PPI. In the first group of rats that received phenylephrine (0 or 0.1 mg/kg), there was no effect of

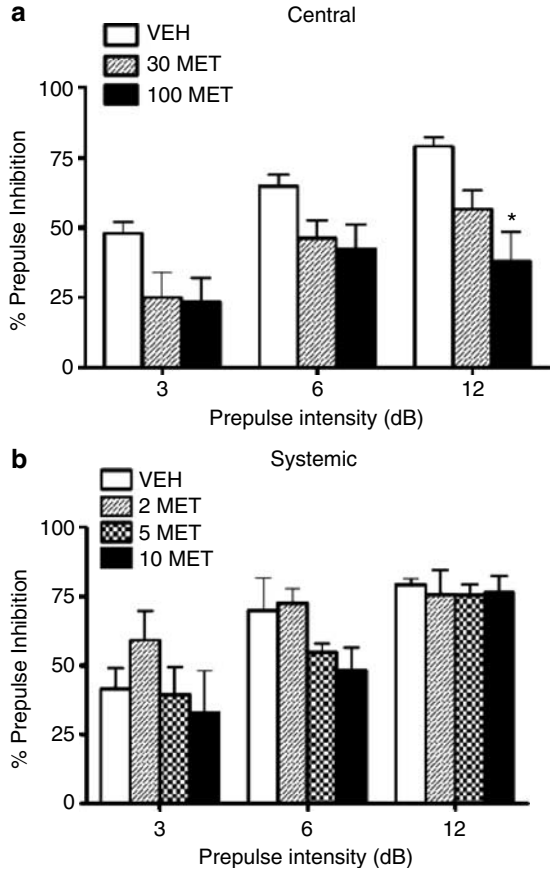

Figure 3 (a and b) Effects of central (a) and systemic (b) administration of the α1 agonist methoxamine on PPI. VEH = vehicle; MET = methoxamine. Prepulse intensity = decibels above background noise. Values are shown as mean ± SEM. Central doses are in μg/5 μl and systemic doses are in mg/kg. *$P < 0.05$, relative to respective vehicle conditions.

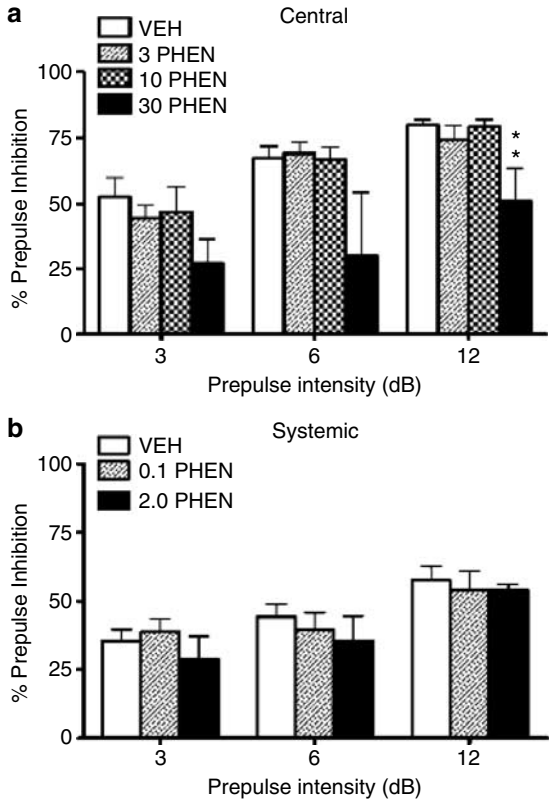

Figure 4 (a and b) Effects of central (a) and systemic (b) administration of the α1 agonist phenylephrine on PPI. VEH = vehicle; PHEN = phenylephrine. Prepulse intensity = decibels above background noise. Values are shown as mean ± SEM. Central doses are in μg/5 μl and systemic doses are in mg/kg. **$P < 0.01$, relative to respective vehicle conditions.

treatment on PPI ($F(1,10) = 0.36$, $P = 0.56$, NS). In the second group of rats that received phenylephrine (0 or 2.0 mg/kg), there was also no effect of treatment on PPI ($F(1,6) = 0.1.9$, $P = 0.21$, NS). Thus, even at a dose that was 20-fold higher than the PPI-disruptive ICV dose, phenylephrine failed to disrupt PPI after IP administration.

Note that a one-way ANOVA was used to compare the vehicle groups of the two different IP phenylephrine studies (0.1 mg/kg study and 2 mg/kg study). This ANOVA revealed that there was no significant difference between the two vehicle groups ($F(1,11) = 0.232$, $P < 0.64$, NS). Therefore, for the sake of brevity, the data from the two vehicle groups are combined in Figure 4b and in Tables 1 and 2.

Effects of Prazosin on Cirazoline-Induced PPI

The results from Experiment 4 are shown in Figure 5. Similar to Experiment 1b, IP cirazoline disrupted PPI as shown by the main effect of treatment on PPI ($F(1,18) = 13.55$, $P < 0.005$). *Post hoc* tests revealed a significant disruption by the 0.5 mg/kg dose at the 6- and 12-dB prepulse levels ($P < 0.01$). A significant effect of pretreatment was also seen ($F(1,18) = 6.38$, $P < 0.05$). Importantly, a significant interaction between pretreatment and treatment was also observed ($F(1,16) = 9.0$, $P < 0.01$), indicating that prazosin pretreatment significantly attenuated the effects of cirazoline on PPI. *Post hoc* analyses revealed that at both the 6- and 12-dB prepulse intensities, the prazosin/cirazoline groups had significantly higher PPI levels than the vehicle/cirazoline condition ($P < 0.05$). PPI values for the prazosin/cirazoline condition were not significantly different from vehicle/vehicle values.

Table 1 Effects of α1 Agonists on Baseline Startle Magnitude

ICV	Vehicle	10 μg/5 μl	25 μg/5 μl	50 μg/5 μl
Cirazoline	256±47	190±34	264±56	269±79
IP	Vehicle	0.25 mg/kg	0.50 mg/kg	0.75 mg/kg
Cirazoline	457±100	363±42	528±81	369±66
ICV	Vehicle	30 μg/5 μl	100 μg/5 μl	
Methoxamine	419±37	264±50	331±51	
IP	Vehicle	2 mg/kg	5 mg/kg	10 mg/kg
Methoxamine	402±69	231±87	157±56	151±76
ICV	Vehicle	3 μg/5 μl	10 μg/5 μl	30 μg/5 μl
Phenylephrine	346±78	289±38	246±54	213±55
IP	Vehicle	0.1 mg/kg	2.0 mg/kg	
Phenylephrine	420±34	510±106	154±11**	
IP Prazosin/	Veh/Veh	Veh/Cir	Praz/Veh	Praz/Cir
IP Cirazoline	414±78	557±93	507±134	530±84

Values are mean±SEM. **$P < 0.01$, compared to vehicle.

Startle Magnitude

The effects of all the drug treatments on startle magnitude are shown in Table 1. Neither IP nor ICV cirazoline affected baseline startle magnitude. Similarly, there was no effect of ICV methoxamine or phenylephrine on startle. However, there was a significant effect of IP phenylephrine on baseline startle magnitude in the high-dose study ($F(1,12) = 24.0$, $P < 0.001$). *Post hoc* analyses indicated that the 2.0 mg/kg dose significantly reduced startle magnitude compared to vehicle values ($P < 0.01$). Similarly, IP methoxamine tended

Table 2 Effects of α1 Agonists on Piloerection

ICV	Vehicle	10 μg/5 μl	25 μg/5 μl	50 μg/5 μl
Cirazoline***	0/9	6/9	9/9	9/9
IP	Vehicle	0.25 mg/kg	0.50 mg/kg	0.75 mg/kg
Cirazoline***	0/9	8/9	9/9	9/9
ICV	Vehicle	30 μg/5 μl	100 μg/5 μl	
Methoxamine	0/5	0/5	0/5	
IP	Vehicle	2 mg/kg	5 mg/kg	10 mg/kg
Methoxamine***	0/5	4/5	5/5	5/5
ICV	Vehicle	3 μg/5 μl	10 μg/5 μl	30 μg/5 μl
Phenylephrine	0/5	0/5	0/5	0/5
IP	Vehicle	0.1 mg/kg	2.0 mg/kg	
Phenylephrine***	0/13	0/6	7/7	
IP Prazosin/	Veh/Veh	Veh/Cir	Praz/Veh	Praz/Cir
IP Cirazoline***	0/5	5/5	0/5	0/5

Values are number of rats showing piloerection over total number of rats per group. ***$P < 0.001$ compared to vehicle or vehicle/vehicle, Cochran's *Q*-test.

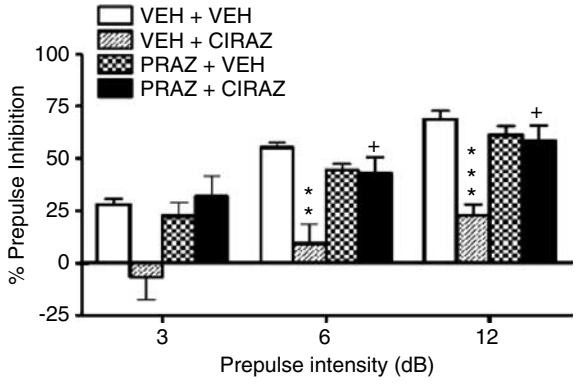

Figure 5 Effects of pretreatment with the α1 antagonist prazosin on cirazoline-induced PPI deficits. VEH = vehicle; CIRAZ = cirazoline; PRAZ = prazosin. Prepulse intensity = decibels above background noise. Values are shown as mean±SEM. Doses are in mg/kg, all given intraperitoneally. **$P < 0.01$, ***$P < 0.005$, relative to vehicle/vehicle condition and $^{+}P < 0.05$, relative to vehicle/cirazoline condition.

to reduce startle magnitude, although this effect did not reach statistical ($F(3,16) = 3.13$, $P < 0.06$). Thus, none of the ICV treatments, all of which disrupted PPI, affected startle magnitude; therefore, the PPI-disrupting effects of central α1 receptor stimulation are independent of changes in baseline startle reactivity.

Piloerection

In order to determine if α1 agonist-induced PPI disruption was related to the well-known autonomic effects of α1 receptor stimulation, the effects of the three α1 noradrenergic agonists on piloerection, an index of autonomic activation (Stephens, 1986), were measured. Rats were scored for the presence or absence of piloerection by an experimenter blind to their treatment condition. The number of rats displaying piloerection per total number of rats in each treatment condition is shown in Table 2. Treatment with cirazoline significantly induced piloerection with either route of administration. Central cirazoline increased piloerection ($P < 0.001$, Cochran's Q-test) with both the medium and the high doses of ICV cirazoline producing piloerection in nine out of nine rats (compared to 0 of nine rats showing piloerection in the vehicle condition). Similarly, all three doses of systemic cirazoline significantly increased the frequency of piloerection ($P < 0.001$), with the low-dose producing piloerection in eight out of nine rats (89%) and both the medium and the high doses causing piloerection in nine out of nine rats (100%). Similarly, in Experiment 4, five out of the five rats that received cirazoline alone displayed piloerection. In contrast, none of the rats receiving prazosin plus cirazoline (0 out of five) showed piloerection, indicating that prazosin reversed the cirazoline effect and confirming that cirazoline-induced piloerection is mediated by α1 receptors. In the case of methoxamine, both the medium and high doses of systemic methoxamine produced piloerection in five out of five rats (100%, $P < 0.01$). In contrast to systemic methoxamine, there was no effect of central methoxamine on piloerection, as none of the rats exhibited piloerection with any central methoxamine dose. Finally, there was an effect of systemic phenylephrine on piloerection. In the group that received 2 mg/kg, seven out of seven rats (or 100%) showed piloerection. There was no effect of central phenylephrine on piloerection. Thus, there was a double-dissociation between piloerection and PPI, as illustrated by the effects of methoxamine and phenylephrine: IP administration produced piloerection but failed to disrupt PPI, while ICV administration did not produce piloerection but did disrupt PPI. Thus, piloerection is neither necessary nor sufficient to disrupt PPI.

DISCUSSION

The present studies provide several important findings regarding α1 adrenergic receptor regulation of PPI. First, central administration of the α1 agonist, cirazoline, disrupted PPI. This disruption was robust and occurred with multiple doses of cirazoline. In addition, in accordance with previous reports, systemic administration of cirazoline disrupted PPI (Carasso *et al*, 1998; Shilling *et al*, 2004; Varty *et al*, 1999). Second, central administration of the α1 agonist methoxamine disrupted PPI. However, systemic methoxamine did not disrupt PPI, even at a dose approximately 30 times higher than the central dose. Third, central administration of the α1 agonist phenylephrine disrupted PPI. As with methoxamine, however, systemic phenylephrine failed to disrupt PPI, even at a dose that was 20 times higher than the PPI-disruptive central dose. Fourth, the α1-selective receptor antagonist prazosin completely blocked all the effects of cirazoline, confirming that these effects are mediated specifically by α1 receptors. Fifth, α1 receptor-mediated PPI disruption is dissociable from changes in baseline startle reactivity as none of the treatments produced a significant change in startle magnitude. Finally, α1 receptor-mediated PPI disruption is dissociable from changes in piloerection, a measure of autonomic activation. Taken together, these results indicate that stimulation of central but not peripheral α1 adrenergic receptors causes a specific disruption of sensorimotor gating that is independent of alterations in baseline startle reactivity or general autonomic activation. To our knowledge, these are the first studies to directly show that the effects of α1 adrenergic receptor stimulation on PPI are centrally mediated.

In the present studies and in previous work, cirazoline has been found to disrupt PPI when given systemically (Carasso *et al*, 1998; Shilling *et al*, 2004; Varty *et al*, 1999). This effect can be blocked with either the α1 antagonist prazosin or the atypical antipsychotic seroquel, but not a dopamine D2 receptor antagonist (Carasso *et al*, 1998). The present study sought to extend this finding by determining whether the effects of cirazoline, which readily crosses the blood-brain barrier, on PPI are mediated by central or peripheral α1 adrenergic receptors. The finding that centrally administered cirazoline disrupted PPI more robustly, and at six-fold lower doses than systemic cirazoline, suggests that the effect is likely mediated by central α1 receptors. Nonetheless, in order to confirm that α1 receptor-induced deficits in PPI are mediated by the CNS and not the periphery, the effects of α1 agonists with low blood–brain barrier permeability were also examined. When comparing the effects of central *vs* systemic administration of methoxamine and phenylephrine, two α1 agonists with low blood–brain barrier permeability (Holz *et al*, 1982; Krulich *et al*, 1982), it was found that both methoxamine and phenylephrine disrupted PPI when administered centrally, but not systemically. In the case of methoxamine, even a dose that was 30-fold higher than the effective central dose failed to disrupt PPI when given systemically, indicating that central and not peripheral α1 receptors mediate the effects of α1 adrenergic agonists on PPI.

It has been shown that augmenting noradrenergic transmission can increase startle magnitude, thus raising the possibility that α1 agonist-induced effects on PPI are simply an artifact of altered baseline startle reactivity. For example, intrathecal infusion of direct postsynaptic adrenergic agonists, including phenylephrine, have been found to increase startle responses in rats (Astrachan and Davis, 1981). Previous studies with cirazoline have shown that systemic administration of this α1 agonist can also increase startle responses, although at a higher dose range than what was utilized in the present studies (Carasso *et al*, 1998;

Varty *et al*, 1999). Further, systemic administration of the α2 adrenergic antagonist, yohimbine, which would increase NE tone, has been shown to facilitate acoustic startle amplitude in both humans and animals (Kehne and Davis, 1985; Krulich *et al*, 1982; Morgan *et al*, 1993). However, a recent study found no effect of yohimbine or another α2 antagonist, atipamezole, on startle (Powell *et al*, 2005), and, in the present studies, high systemic doses of phenylephrine and methoxamine actually decreased baseline startle magnitude. Thus, the regulation of startle magnitude by manipulations that increase NE transmission remains unclear.

Importantly, in this study we found that none of the α1 agonists altered startle magnitude after central infusion even though they disrupted PPI with this route of administration. Moreover, the manipulations that affected startle magnitude (IP phenylephrine and IP methoxamine) failed to influence PPI. Taken together, there results indicate that α1 receptor-mediated changes in PPI are completely dissociable from changes in startle magnitude. In concert with this dissociation is the recent finding that two different α2 antagonists, which could increase NE via blockade of inhibitory autoreceptors, were found to disrupt PPI without affecting baseline startle reactivity (Powell *et al*, 2005). Therefore, within the dose ranges utilized in the present studies, stimulation of central α1 receptors specifically and selectively disrupts this form of plasticity of the startle response (ie PPI) rather than the startle reflex itself.

Another issue that could compromise the interpretation of the present findings is that enhanced NE transmission can cause sympathetic arousal (Cooper *et al*, 2003), leading to the possibility that the α1 agonist-induced PPI deficits observed in the present study were secondary to the recruitment of autonomic activation. In order to test the hypothesis that α1 agonist-induced PPI deficits are associated with increased sympathetic tone, the effects of the drugs on piloerection, an index of autonomic sympathetic activity (Stephens, 1986) was examined. Piloerection is believed to involve the spinal cord (Roberts and Foglesong, 1988) and postganglionic sympathetic fibers (Gibbins, 1992) and is part of the constellation of autonomic effects, such as increased heart rate and blood pressure, that are commonly observed with enhanced NE transmission (Hein *et al*, 1999; Lahdesmaki *et al*, 2002; Minneman *et al*, 1981; Philipp and Hein, 2004). Several lines of evidence implicate the noradrenergic system in the regulation of piloerection. Mice lacking the α2a receptor and thus displaying a phenotype of increased noradrenergic function have an increased frequency of piloerection (Lahdesmaki *et al*, 2002). Conversely, the α1 antagonist prazosin blocks fear-induced piloerection in mice (Masuda *et al*, 1999). Similarly, mice who lack the gene for dopamine-β-hydroxylase (the enzyme that converts dopamine into NE) and are thus unable to synthesize NE show a reduction in piloerection (Thomas and Palmiter, 1997). Thus, as with other indices of autonomic activation such as increased heart rate, manipulations that increase NE tone generally elicit piloerection, whereas those that reduce NE transmission decrease piloerection. Several studies show that methoxamine produces piloerection in humans (Duke *et al*, 1963; Radley *et al*, 2001; Tomasi *et al*, 2005). Consistent with this pattern, it was found in the present studies that direct α1 agonists elicited piloerection. Cirazoline-elicited piloerection when administered either centrally or systemically; both routes of administration also led to PPI disruption. In the case of methoxamine and phenylephrine, however, a critical dissociation between piloerection and PPI was observed. Systemic administration of these drugs produced piloerection but failed to affect PPI whereas central infusion disrupted PPI but failed to induce piloerection. Taken together, these findings indicate that different populations of α1 receptors may modulate piloerection and PPI, with piloerection likely being mediated by α1 receptors in the periphery and spinal cord and PPI being regulated by α1 receptors in the brain. The finding that ICV infusion of cirazoline-elicited piloerection is likely due to the activation of peripheral α1 receptors, as this drug is highly lipophilic and may cross the blood-brain barrier after central administration, unlike methoxamine and phenylephrine, which elicited piloerection only after IP injection. Thus, it appears that autonomic arousal (as indexed by piloerection) is neither necessary nor sufficient to disrupt PPI after α1 agonist administration.

It is important to note that cirazoline, in addition to acting on the noradrenergic system, also has high affinity for imidazoline receptors (Angel *et al*, 1995; Bricca *et al*, 1988, 1989; Wikberg and Uhlen, 1990). Imidazoline receptors have been shown to be important in mediating the hypotensive effects of antihypertensive drugs such as clonidine (Head, 1995). In the case of cirazoline, it has been shown that infusions of cirazoline into the nucleus reticularis lateralis of the medulla oblongata results in a hypotensive effect that is independent of α receptors (Bousquet *et al*, 1984). Thus, it appears that cirazoline produces some of its effects through central imidazoline sites and raises the possibility that the PPI-disruptive effects of this compound are mediated through imidazoline rather than α1 receptors. This possibility is unlikely, however, given that both methoxamine and phenylephrine, which have negligible affinity for imidazoline receptors, potently disrupt PPI after central infusion. In addition, the α1-selective antagonist prazosin, which also lacks affinity for imidazoline sites (Angel *et al*, 1995; Wikberg and Uhlen, 1990) completely reverses cirazoline-induced deficits in PPI (Carasso *et al*, 1998). Thus, the PPI-disruptive effects of α1 agonists such as cirazoline are due to actions at α1 and not imidazoline receptors.

Despite the well-known role of NE in processes related to arousal, attention, and cognitive function (Arnsten *et al*, 1998; Aston-Jones *et al*, 1999; Berridge and Waterhouse, 2003), surprisingly few studies have examined the role of the adrenergic system in modulating PPI. A few studies using transgenic mice have shown that mice lacking the α2C receptor have disrupted PPI (Sallinen *et al*, 1998) while mice lacking the α1D receptor or the α2A receptor do not show the same magnitude of disruption in PPI after psychotomimetic drug administration as wild-type mice (Lahdesmaki *et al*, 2004; Mishima *et al*, 2004). It must be pointed out though, that a recent study examined the effects of the α2 antagonist yohimbine on PPI and found that while yohimbine disrupts PPI, this effect may in part be due to its actions at serotonin-1A receptors (Powell *et al*, 2005).

Our previous work using acute drug administration as in the present study has indicated that α1 receptors may in

part mediate the PPI-disrupting effects of psychotomimetic drugs such as PCP and dizolcipine and may represent an important mechanism through which atypical antipsychotics block these sensorimotor gating deficits, since the α1 receptor antagonist prazosin mimics the ability of clozapine but not traditional neuroleptics to block *N*-methyl-D-asparate antagonist-induced PPI deficits (Bakshi and Geyer, 1997, 1999). Consistent with these results is the finding that stimulation of α1 receptors disrupts PPI (Carasso *et al*, 1998; Shilling *et al*, 2004; Varty *et al*, 1999). While clearly indicating an important role for α1 receptors in PPI, these studies did not determine if α1 receptor effects on PPI are mediated in the CNS, and failed to address the possibility that the PPI-disruptive effect of α1 receptor stimulation may be secondary to the recruitment of other α1-mediated effects such as autonomic activation. Our findings clarify these issues and significantly extend this literature regarding noradrenergic modulation of PPI by showing that α1 receptor-mediated PPI disruptions are produced specifically through central rather than peripheral receptors and that these disruptions are independent of changes in baseline startle reactivity or autonomic activation, which are two other well-known effects associated with noradrenergic receptor stimulation. Thus, the present studies corroborate the notion that the NE system modulates PPI and are the first to systematically demonstrate that CNS α1 receptors selectively and specifically disrupt sensorimotor gating.

The finding that central α1 receptor stimulation disrupts sensorimotor gating is syntonic with several prominent theories on the regulation of cognitive processing by the noradrenergic system. For many years, the locus coeruleus (LC)-NE system has been known to influence attention and cognition functioning, participating in the maintenance of states of high arousal and vigilance, and contributing to general processes underlying learning and memory (Aston-Jones *et al*, 1999; Berridge and Waterhouse, 2003; Everitt *et al*, 1983; Foote *et al*, 1983; Langlais *et al*, 1993; Rajkowski *et al*, 1994). For instance, it has been proposed that the regulation of attention by LC-NE neurons has an inverted-U-shaped profile, with either hypo- or hyperactivity of tonic LC-NE discharge rates disrupting the ability to maintain focused attention (Aston-Jones *et al*, 1999). Arnsten (2004) have proposed that high levels of NE in the prefrontal cortex, which could result from a hyperactivation of the LC-NE system, act on α1 receptors to disrupt cognition. For example, α1 receptor stimulation within the prefrontal cortex with cirazoline or phenylephrine produces impairments in tasks of working memory in rats and nonhuman primates (Arnsten and Jentsch, 1997; Arnsten *et al*, 1999; Mao *et al*, 1999). A similar mechanism could govern the regulation of PPI by the LC-NE system, with hyperactivation of LC resulting in the stimulation of α1 receptors via enhanced NE release in terminal regions. Importantly, disruption of PPI and working memory are two of the cardinal features observed in schizophrenia patients, and are thought to provide operational measures for the information-processing deficits that are hypothesized to contribute to the pathophysiology of this illness (Arnsten, 2004; Braff and Light, 2004). The present results thus further strengthen the notion that central α1 receptors may regulate cognitive processes that are deficient in psychiatric illnesses such as schizophrenia.

It is interesting to note that elevations in NE have been found in the cerebrospinal fluid, plasma, or brain tissue of schizophrenia patients, an observation that offers some evidence for disturbances of the noradrenergic system within this psychiatric population (Breier *et al*, 1990; Hornykiewicz, 1982; van Kammen *et al*, 1989a). In fact, some have proposed that the noradrenergic system may be an important component in the therapeutic actions of certain antipsychotic medications (Baldessarini *et al*, 1992; Breier, 1994; Cohen and Lipinski, 1986; Prinssen *et al*, 1994; Svensson *et al*, 1995). Several disorders with deficient sensorimotor gating, such as ADHD and PTSD have hypothesized pathology within the NE system (Aston-Jones *et al*, 1999; Southwick *et al*, 1999), and there is some evidence that administration of clonidine, which decreases noradrenergic transmission from the LC, improves conduct symptoms in patients with ADHD and global symptoms in patients with PTSD (Hazell and Stuart, 2003; Kinzie and Leung, 1989; Porter and Bell, 1999). In the case of schizophrenia, a few studies have shown that clonidine may be beneficial in treating psychotic symptoms (Freedman *et al*, 1982; Maas *et al*, 1995; van Kammen *et al*, 1989b). However, several studies have reported no effect of clonidine in schizophrenic patients (Jimerson *et al*, 1980; Simpson *et al*, 1967; Sugerman, 1967), but this discrepancy has been attributed to patient selection (ie antipsychotic drug responsiveness) and differences in dosage of clonidine (Freedman *et al*, 1982). Insofar as deficient PPI represents an operational measure of information-processing deficits associated with schizophrenia and has been proposed as an endophenotype for this and other illnesses involving deficient sensorimotor gating (Braff and Freedman, 2002; Braff *et al*, 2001), the present findings suggest that dysregulation of neurotransmission at CNS α1 receptors may contribute to the information-filtering abnormalities that are observed in these illnesses.

In summary, the present findings indicate that the noradrenergic system, in part acting through central α1 receptors, plays an important role in modulating PPI. It was found that central administration of three different α1 agonists produced a disruption in PPI, while systemic administration of α1 agonists with low brain permeability did not produce any effect on PPI. In addition, effects of the α1 drugs on baseline startle magnitude and piloerection, two responses that commonly result from α1 receptor stimulation, were dissociable from effects on PPI. Thus, the current results for the first time indicate a CNS-mediated disruption specifically of sensorimotor gating by α1 receptor stimulation. Future studies are needed to understand the neuroanatomical regions subserving the effects of noradrenergic drugs on PPI as well as the contributions of the different noradrenergic receptor subtypes. Nonetheless, the present studies represent an important first step in characterizing the neural substrates through which the NE system regulates sensorimotor gating. Ultimately, this work may lead to an improved understanding of how a system that has been relatively overlooked in studies of PPI may participate in the information-processing deficits that are observed in schizophrenia and other disorders of deficient information filtering.

ACKNOWLEDGEMENTS

These studies were supported by NIMH Grant #42228, NRSA T32 GM0757, the Scottish Rite Schizophrenia Research Fellowship Program (to KMA), the NARSAD Young Investigator Award program (to VPB), and a Howard Hughes Medical Institute Faculty Development award (to VPB).

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