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Ventral Striatal Noradrenergic Mechanisms Contribute to Sensorimotor Gating Deficits Induced by Amphetamine

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The psychotomimetic drug D-amphetamine (AMPH), disrupts prepulse inhibition (PPI) of the startle response, an operational measure of sensorimotor gating that is deficient in schizophrenia patients. Historically, this effect has been attributed to dopaminergic substrates; however, AMPH also increases norepinephrine (NE) levels, and enhancement of central NE transmission has been shown recently to disrupt PPI. This study examined the extent to which NE might participate in AMPH-induced disruptions of PPI and increases in locomotor activity, another classic behavioral effect of AMPH, by determining whether antagonism of postsynaptic NE receptors blocked these effects. Separate groups of male Sprague–Dawley rats received either the α1 receptor antagonist, prazosin (0, 0.3, 1 mg/kg), or the β receptor antagonist timolol (0, 3, 10 mg/kg) before administration of AMPH (0 or 1 mg/kg) before testing for PPI or locomotor activity. As an initial exploration of the anatomical substrates underlying possible α1 receptor-mediated effects on AMPH-induced PPI deficits, the α1 receptor antagonist terazosin (0 or 40 μg/0.5 μl) was microinfused into the nucleus accumbens shell (NAccSh) in conjunction with systemic AMPH administration before startle testing in a separate experiment. Prazosin, but not timolol, blocked AMPH-induced hyperactivity; both drugs reversed AMPH-induced PPI deficits without altering baseline startle responses. Interestingly, AMPH-induced PPI deficits also were partially blocked by terazosin in NAccSh. Thus, behavioral sequelae of AMPH (PPI disruption and hyperactivity) may be mediated in part by NE receptors, with α1 receptors in NAccSh possibly having an important role in the sensorimotor gating deficits induced by this psychotomimetic drug.

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INTRODUCTION

Prepulse inhibition (PPI) refers to the reduction in the magnitude of the startle response that normally is observed when a low intensity prestimulus is presented immediately before a startling stimulus (Graham, 1975; Hoffman and Ison, 1980; Ison and Hoffman, 1983), and is used as a measure of sensorimotor gating. Several decades of research have established deficient PPI as an exemplar of the information-processing deficits that are observed in multiple psychiatric illnesses, and PPI disturbances are a well-accepted endophenotype of schizophrenia (Braff *et al*, 2001b, 2008). To identify the neurochemical modulators and neuroanatomical circuits underlying these clinically observed deficits in sensorimotor gating, the neural substrates of PPI have been analyzed extensively in animal models (Geyer, 2008; Swerdlow *et al*, 2008).

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One method for mimicking clinically manifested PPI deficits in rats is through the administration of psychotomimetic drugs such as amphetamine (AMPH). AMPH has long been known to produce psychotic symptoms in humans that closely resemble the symptoms of schizophrenia (Charalampous and Hug, 1963; Kokkinidis and Anisman, 1981; Snyder, 1973), and also can disrupt PPI in humans (Hutchison and Swift, 1999; Hutchison *et al*, 1999; Kumari *et al*, 1998), although see (Swerdlow *et al*, 2002). In rodents, AMPH disrupts PPI when given systemically (Kinney *et al*, 1999; Mansbach *et al*, 1988; Ott and Mandel, 1995; Ralph *et al*, 1999; Sills, 1999; Swerdlow *et al*, 2006) or directly into the brain (Wan *et al*, 1995; Wan and Swerdlow, 1996). To date, these effects have been attributed to the ability of AMPH to release dopamine (DA), because it is well documented that direct DA agonists disrupt PPI and DA receptor antagonists reverse these deficits (Mansbach *et al*, 1988; Swerdlow *et al*, 1986, 1994; Wan and Swerdlow, 1993). Clearly, DA receptors have a critical role in the PPI-disruptive effects of AMPH, given that AMPH-induced PPI deficits are reversed by DA receptor antagonists (Swerdlow *et al*, 2006).

Nevertheless, AMPH also increases extracellular levels of norepinephrine (NE) (Carr and Moore, 1969; Kuczenski and

Segal, 1992; Robertson *et al*, 2009) and some of the behavioral effects of AMPH that previously were attributed to its actions on DA systems have since been shown to also require stimulation of NE receptors (Auclair *et al*, 2004; Drouin *et al*, 2002a, b). For example, antagonism of $\alpha 1$ noradrenergic receptors blocks AMPH-induced hyperactivity (Blanc *et al*, 1994; Dickinson *et al*, 1988), and β NE receptors mediate the effects of AMPH on arousal (Berridge and Morris, 2000). Yet, whether NE receptors mediate AMPH-induced PPI deficits remains to be determined.

Newly emerging evidence supports the regulation of PPI by NE. The NE receptor agonist, cirazoline, disrupts PPI (Carasso *et al*, 1998; Shilling *et al*, 2004; Varty *et al*, 1999) through activation of central $\alpha 1$ receptors (Alsene *et al*, 2006). Conversely, antagonism of $\alpha 1$ NE receptors blunts the PPI-disruptive effects of other psychotomimetic drugs that also indirectly increase NE levels, such as phencyclidine and cocaine (Bakshi and Geyer, 1997; van der Elst *et al*, 2006). Mice lacking $\alpha 2A$ NE receptors show exaggerated deficits in PPI after administration of AMPH (Lahdesmaki *et al*, 2004); as $\alpha 2$ receptors function primarily as autoreceptors whose blockade or removal would result in an increase in NE levels (Hein *et al*, 1999; Starke *et al*, 1989), this finding is consistent with the notion that increasing central NE transmission reduces PPI. Thus, it is possible that the well-documented PPI-disrupting effects of AMPH could in part be mediated by indirect stimulation of postsynaptic NE receptors as a result of the potent NE-releasing properties of AMPH (Robertson *et al*, 2009).

NE receptors are classified into three main subtypes: $\alpha 1$, $\alpha 2$, and β, with $\alpha 1$ and β receptors as the principal moieties that mediate postsynaptic effects of NE transmission (Pupo and Minneman, 2001). The present experiments tested the hypothesis that AMPH produces its behavioral effects through enhanced NE transmission by determining if blockade of postsynaptic NE receptors with either the $\alpha 1$ antagonist prazosin or the β antagonist timolol would prevent AMPH-induced deficits in PPI or AMPH-induced hyperactivity, which is another well-known consequence of AMPH administration in rodents (Berridge, 2006). As an initial exploration of putative neuroanatomical substrates for NE mediation of AMPH effects on PPI, the ability of an $\alpha 1$ receptor antagonist microinfused into the nucleus accumbens shell (NAccSh) to block AMPH-induced PPI deficits was also examined, because NAccSh is known to mediate AMPH-induced PPI deficits and is also heavily innervated by NE-containing terminals (Berridge *et al*, 1997; Delfs *et al*, 1998; Wan and Swerdlow, 1996). To the best of our knowledge, these studies are the first to systematically examine if forebrain NE receptors contribute to the sensorimotor gating deficits produced by AMPH.

MATERIALS AND METHODS

Subjects

In total, 158 experimentally naïve male Sprague–Dawley rats (Harlan Laboratories, Madison WI, USA) were housed in pairs in clear polycarbonate cages in a light- and temperature-controlled vivarium with lights on at 0700 hours and off at 1900 hours; all testing occurred between 1000 hours and 1600 hours. Food and water were available *ad libitum*. On arrival, rats were acclimated to the vivarium for 1 week with daily handling; no procedures or tests occurred during that time. Facilities and procedures complied with animal use and care guidelines from the National Institutes of Health of the United States, and were approved by the Institutional Animal Care and Use Committee of the University of Wisconsin.

Startle and PPI Testing

Startle chambers (San Diego Instruments, San Diego, CA, USA) consisted of nonrestrictive Plexiglas cylinders resting inside a ventilated and illuminated sound-attenuating cabinet. A high-frequency loudspeaker inside the chamber produced both a continuous background noise and the various acoustic stimuli. The whole-body startle response 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. Sound levels were measured using the dB(A) scale.

The startle session used 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 session. The test session 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, 9, or 15 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). There were 16 presentations of each of the Prepulse + Pulse trials, 24 Pulse-Alone trials, and 16 No Stimulus trials, with an average of 15 s between consecutive trials. The first and last four trials of the session were Pulse-Alone presentations that were not included in PPI or startle magnitude calculations, but were used to stabilize average startle responses for the remainder of the session, since the most marked habituation of startle responses occurs with the first several presentations of the startling stimulus (Geyer *et al*, 1990).

Activity Cages

Locomotion and rearing were measured using a Photobeam Activity System from San Diego Instruments that consisted of wire-floor clear plastic cages (with no food or water) surrounded by a grid of photobeams. Interruptions in the horizontal beams provided a measure of cage crossings (locomotion) and breaks in the vertical beams measured rearing.

Surgery and Microinfusions

For experiment 5, rats were anesthetized with a xylazine/ketamine mixture (80 mg ketamine and 12 mg xylazine per ml of the mixture; Phoenix Scientific, St Joseph, MO, USA) and secured in a stereotaxic frame (Kopf Instruments, Tujunga, CA, USA). Stainless steel cannulae (23 gauge, Small Parts, Miami Lakes, FL, USA) were implanted and affixed to the skull with dental cement (Lang Dental Mfg,

Wheeling, IL, USA) and anchoring screws (Plastics One, Roanoke, VA, USA), and were aimed bilaterally at the NAccSh using the atlas of Pellegrino and Cushman (1967), with nosebar set to 5.0 mm above interaural zero. Surgical coordinates from bregma were: +3.2 mm AP; ±1.0 mm LM; −5.2 mm DV (with injectors extending an additional 2.5 mm beyond cannulae tips for a final DV coordinate of −7.7). Wire stylets were placed in the cannulae to prevent blockage. Rats recovered for a week with daily health checks and handling before any procedures or testing occurred.

For microinfusions, stylets were removed, cannulae were cleaned with a dental broach (Henry Schein, Melville, NY, USA), and stainless steel injectors were inserted (30-gauge, Small Parts). The injectors were attached with polyethylene tubing (PE-10, Becton Dickinson, Sparks, MD, USA) to 10-μl glass Hamilton syringes (Hamilton, Reno, NV, USA) mounted on a microdrive pump (Harvard Apparatus, Holliston, MA, USA). Microinfusions were administered at a rate of 0.32 μl/min with a final volume of 0.5 μl per side. Injectors were left in place for one additional minute before stylets were replaced to allow for absorption of the infusate into the tissue. Several days before the experiment, rats received a mock infusion in which injectors were lowered but no infusate was delivered to acclimate them to the infusion procedure.

Drugs

D-AMPH sulfate, prazosin hydrochloride, timolol maleate, and terazosin hydrochloride were obtained from Sigma (St Louis, MO, USA); all drugs except for prasozin were dissolved in sterile isotonic saline. Prazosin was dissolved with sonication in a vehicle solution comprised of 95% distilled water plus 5% DMSO (Sigma). This solution was used as the vehicle injection for all prazosin experiments.

Experimental Design

Five experiments were conducted using separate groups of experimentally naïve rats for each experiment. For all PPI studies, rats underwent three baseline startle/PPI tests, with the final baseline occurring 2–3 days before the experiment to create equally matched treatment groups (on the basis of PPI and startle magnitude) for subsequent drug testing; for experiment 5 (NAccSh), the mock infusion was conducted immediately before this final baseline startle/PPI test. Similarly, for all locomotor activity studies, rats were habituated for 2 h to the photocell cages 2–3 days before the experiment, and equally matched treatment groups were designated for the subsequent drug testing on the basis of total activity levels from the habituation day. Doses and injection parameters for prazosin, AMPH, timolol, and terazosin were based on previous experiments in which these drugs were found to affect PPI or antagonize behavioral effects induced by agonists for their respective receptors (Bakshi and Geyer, 1997; Colussi-Mas *et al*, 2005).

Experiment 1: Prazosin/AMPH/PPI. Rats ($N=7$–11 per dose) received intraperitoneal (IP) injection of the $\alpha 1$ receptor antagonist prazosin (vehicle, 0.3, or 1 mg/kg) 25 min before a subcutaneous (SC) injection of saline or AMPH (1 mg/kg) and were tested in startle chambers 5 min later. After 1 week, the protocol was repeated, but within each prazosin dose group, rats that had previously received saline received AMPH and vice versa. Thus, prazosin dose was a between-subjects factor, and AMPH treatment was within-subjects.

Experiment 2: Timolol/AMPH/PPI. Using the same cross-over design as experiment 1, rats ($N=12$–15 per dose) received IP injection of the β NE receptor antagonist, timolol (0, 3, or 10 mg/kg) 5 min before SC AMPH injection (0, 1 mg/kg), and were tested in startle chambers 5 min later.

Experiment 3: Prazosin/AMPH/activity. Rats ($N=6$–7 per group, with pretreatment and treatment as between-subjects factors) were placed in activity cages for 30 min, then given IP injection of prazosin (0, 0.3, or 1 mg/kg), placed back in the activity cages, and 25 min later given SC injection of AMPH (0 or 1 mg/kg). Motor activity was then measured for 60 min.

Experiment 4: Timolol/AMPH/activity. Using the same design as experiment 3, rats ($N=7$–9 per group) were placed in activity cages for 50 min, given IP injections of timolol (0, 3, or 10 mg/kg), placed back in activity cages, and 5 min later given SC injection of AMPH (0 or 1 mg/kg) before measurement of motor activity for 60 more minutes.

Experiment 5: Terazosin in NAccSh/AMPH/PPI. Rats ($N=12$) received SC injections of AMPH (0 or 1 mg/kg) followed by intra-NAccSh infusion of terazosin (0 or 40 μg/0.5 μl; used because of its solubility in isotonic saline) and then immediately were tested in startle chambers. In a counterbalanced order over four test days, all rats received all four pretreatment/treatment combinations, with at least 96 h separating consecutive tests.

Data Analysis

For PPI 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}. For experiments 1–2, startle data were calculated with two-way analysis of variance (ANOVA) using pretreatment (prazosin or timolol) as a between-subjects factor and treatment (AMPH) as a within-subjects factor. PPI data were analyzed using these same factors in a three-way ANOVA with prepulse as an additional (within-subjects) factor. For experiment 5, all factors (pretreatment, treatment, prepulse intensity) were within-subjects.

Total cage crossings (locomotion) and rears were calculated in 15-min intervals over the 2-h test session. The data from the last four intervals (last 60 min of the session) corresponded to post-AMPH injection time-points, and were analyzed with separate three-factor ANOVAs with

time (intervals) as the repeated measure and pretreatment and treatment as between-subjects variables. For all experiments, *post hoc* analyses were conducted using Newman–Keuls tests, with α level set at 0.05.

Histological verification of injector placements was carried out by an experimenter that was blind to the behavioral data to confirm localization of microinfusions in experiment 5 to the NAccSh. Rats were perfused transcardially with 0.9% saline followed by 10% formalin; brains were removed, sliced (60 μm), and stained with Cresyl violet; and sections were examined under a light microscope. Final sample size for the behavioral data reflects the omission of one rat whose placements were found to fall outside of the shell of the accumbens.

RESULTS

Experiment 1: The α1 NE Receptor Antagonist Prazosin Reverses AMPH-Induced PPI Deficits

As expected, there was a main effect of prepulse intensity ($F(2, 22) = 110$, $P < 0.001$), which is a well-known parametric feature of PPI whereby increasing prepulse intensities elicit higher levels of PPI (Braff *et al*, 2001a). For the sake of brevity, reporting of this main effect, which was observed in all of the PPI experiments, is not repeated throughout the results section. Figure 1 illustrates the effects of prazosin and AMPH on PPI. There was a main effect of AMPH treatment ($F(1, 22) = 11.40$, $P < 0.003$), with AMPH producing a robust decrease in PPI at all three prepulse intensities ($P < 0.01$–$P < 0.001$) (Figure 1a). There was no main effect of prazosin pretreatment ($F(2, 22) = 1.4$, NS), but there was a significant interaction between prazosin pretreatment and AMPH treatment on PPI ($F(2, 22) = 6.2$, $P < 0.008$). Subsequent *post hoc* tests showed that the low dose of prazosin (0.3 mg/kg) reversed AMPH-induced deficits in PPI at the 9- and 15-dB prepulse intensities ($P < 0.05$), with PRAZ + AMPH PPI levels not differing significantly from those of the VEH + VEH condition.

The effects of prazosin and AMPH on baseline startle responses are shown in Figure 1b. There was a main effect of AMPH treatment ($F(1, 22) = 62.5$, $P < 0.001$) with AMPH producing a decrease in startle magnitude ($P < 0.001$), which has been reported previously (Swerdlow *et al*, 2001). Significant pretreatment or pretreatment × treatment effects were not observed. Thus, prazosin did not alter the AMPH-induced reduction in startle magnitude, which taken together with the PPI data indicate that the reversal of AMPH-induced PPI deficits by prazosin is dissociable from effects on baseline startle magnitude.

Experiment 2: The β NE Receptor Antagonist Timolol Reverses AMPH-Induced Deficits in PPI

The results from the timolol/AMPH experiment are shown for PPI in Figure 2a and for startle responses in Figure 2b. There was a main effect of AMPH treatment ($F(1, 39) = 9.1$, $P < 0.005$) with AMPH significantly reducing PPI at multiple prepulse intensities ($P < 0.05$–$P < 0.001$). There was no main effect of timolol pretreatment ($F(2, 39) = 1.3$, NS), but there was a significant interaction between timolol pretreatment × AMPH treatment ($F(2, 39) = 3.3$, $P < 0.046$). *Post hoc* analyses indicated that like prazosin, the lower dose of timolol (3 mg/kg) also reduced AMPH-induced PPI deficits at multiple prepulse intensities ($P < 0.05$).

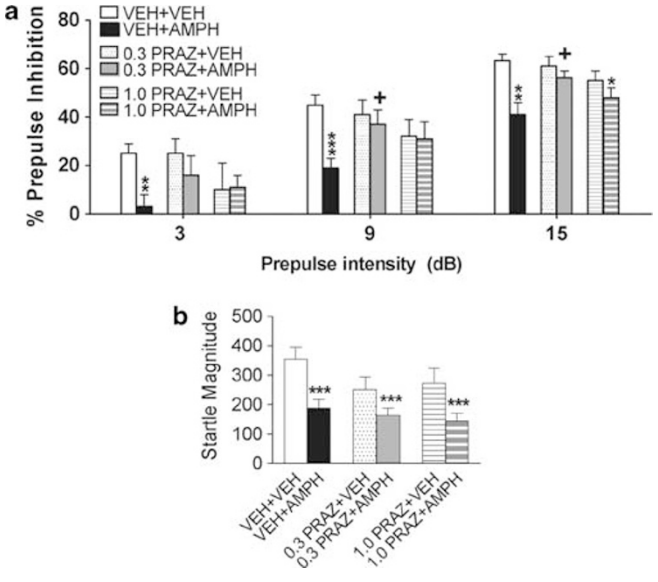

Figure 1 Effects of pretreatment with the α1 receptor antagonist, prazosin (PRAZ), on (a) prepulse inhibition and (b) startle magnitude after amphetamine (AMPH) administration. Values represent means ± SEM for each drug condition. Doses are in mg/kg. Prepulse intensity indicates decibels above the background noise level. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ relative to VEH + VEH condition; $^{+}P < 0.05$ relative to VEH + AMPH condition.

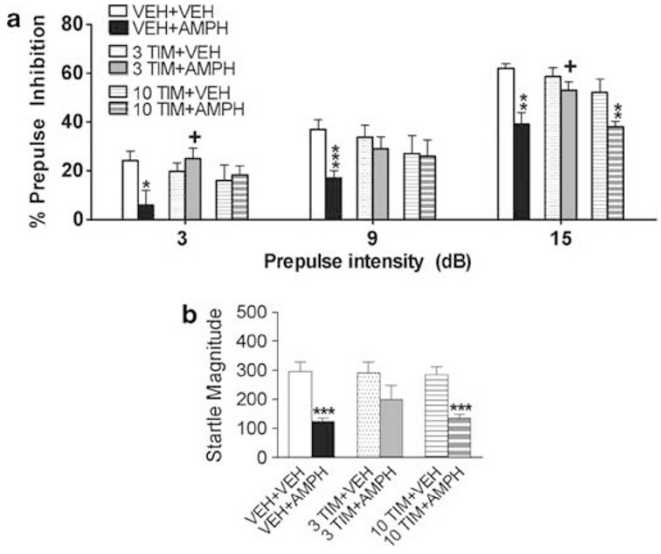

Figure 2 Effects of pretreatment with the β receptor antagonist, timolol (TIM), on (a) prepulse inhibition and (b) startle magnitude after amphetamine (AMPH) administration. Values represent means ± SEM for each drug condition. Doses are in mg/kg. Prepulse intensity indicates decibels above the background noise level. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ relative to VEH + VEH condition; $^{+}P < 0.05$ relative to VEH + AMPH condition.

There was a significant main effect of AMPH on baseline startle ($F(1,39)=76.3$, $P<0.001$), with AMPH producing a decrease in baseline startle magnitude compared with the vehicle + vehicle condition ($P<0.001$). There was no main effect of timolol pretreatment on baseline startle ($F(2,39)=0.5$, NS) nor a significant timolol pretreatment × AMPH treatment interaction ($F(2,39)=2.3$, NS). Thus, timolol did not block the decrease in baseline startle magnitude caused by AMPH, but like prazosin, did reverse AMPH-induced PPI deficits.

Experiment 3: Prazosin Reduces AMPH-Induced Hyperactivity

The effects of prazosin and AMPH on locomotion (horizontal beam breaks that provide a measure of cage crossings) and rearing (vertical beam breaks) are shown in Figures 3a and b, respectively. There was a main effect of AMPH treatment on locomotion ($F(1,35)=87.8$, $P<0.001$), with AMPH increasing cage crossings (VEH + AMPH group *vs* VEH + VEH group) at all timepoints after its administration ($P<0.001$). There was also a main effect of prazosin pretreatment ($F(2,35)=3.8$, $P<0.032$). Importantly, there was a significant interaction between prazosin pretreatment and AMPH treatment ($F(2,35)=4.1$, $P<0.026$). There was a main effect of time ($F(3,105)=3.9$, $P<0.01$) that likely arose from the significant interaction between time and AMPH treatment ($F(3,105)=5.4$, $P<0.002$). There was no significant interaction between time and prazosin pretreatment ($F(6,105)=0.3$, NS) and no three-way interaction between time, prazosin pretreatment, and AMPH treatment ($F(6,105)=0.8$, NS). Subsequent *post hoc* tests revealed that the high dose of prazosin (1.0 mg/kg) partially reversed AMPH-induced increases in locomotion at all timepoints after AMPH administration such that the 1.0 PRAZ + AMPH group had significantly lower values than the VEH + AMPH group ($P<0.05$ at all timepoints), but still had significantly higher values than the VEH + VEH group ($P<0.05$). The lower dose of prazosin had no effect.

Similar to the profile observed with locomotion, there was a main effect of AMPH treatment on rearing ($F(1,35)=58.6$, $P<0.001$), with AMPH increasing the number of rears at all four post-injection timepoints ($P<0.001$). There was also a main effect of prazosin pretreatment ($F(2,35)=13.0$, $P<0.001$), and a significant interaction between prazosin pretreatment and AMPH treatment ($F(2,35)=12.1$, $P<0.001$), indicating that prazosin also reversed AMPH-induced increases in rearing. There was no significant main effect of time ($F(3,105)=0.4$, NS), nor significant interactions between time and prazosin pretreatment ($F(6,105)=0.6$, NS) nor a three-way time × prazosin pretreatment × AMPH treatment interaction ($F(6,105)=1.1$, NS); there was a significant interaction between time and AMPH treatment ($F(3,105)=5.7$, $P<0.005$). Subsequent *post hoc* tests showed that there was a partial reversal of AMPH-induced increases in rearing by the low dose of prazosin (0.3 mg/kg) ($P<0.05$) and a full reversal by the high dose (1.0 mg/kg) at all four timepoints ($P<0.01$).

Experiment 4: Timolol Does not Reduce AMPH-Induced Hyperactivity

The results from experiment 4 are shown in Figure 4 and divided into locomotion (Figure 4a) and rearing (Figure 4b). In the case of locomotion, there was a significant main effect of AMPH treatment ($F(1,42)=381$, $P<0.001$). Timolol pretreatment, however, had no effect on locomotion as there was no significant main effect of pretreatment ($F(2,42)=1.7$, NS), nor an interaction between timolol pretreatment and AMPH treatment ($F(2,42)=1.8$, NS). There was a main effect of time ($F(3,126)=5.9$, $P<0.001$) and significant interactions between time and timolol pretreatment ($F(6,126)=2.2$, $P<0.044$) and time and AMPH treatment ($F(3,126)=3.7$, $P<0.014$), but there was no significant time × pretreatment × treatment interaction ($F(6,126)=1.2$, NS). *Post hoc* analyses showed that all groups receiving AMPH had higher levels of locomotion than the VEH + VEH group ($P<0.001$), and that there were no differences between timolol + AMPH groups and the VEH + AMPH group.

The profile for rearing was similar, with AMPH-induced hyperactivity reflected in the significant main effect of AMPH treatment ($F(1,42)=129.4$, $P<0.001$). There were no effects of timolol pretreatment on rearing ($F(2,42)=1.7$, NS) nor were there significant interactions between timolol

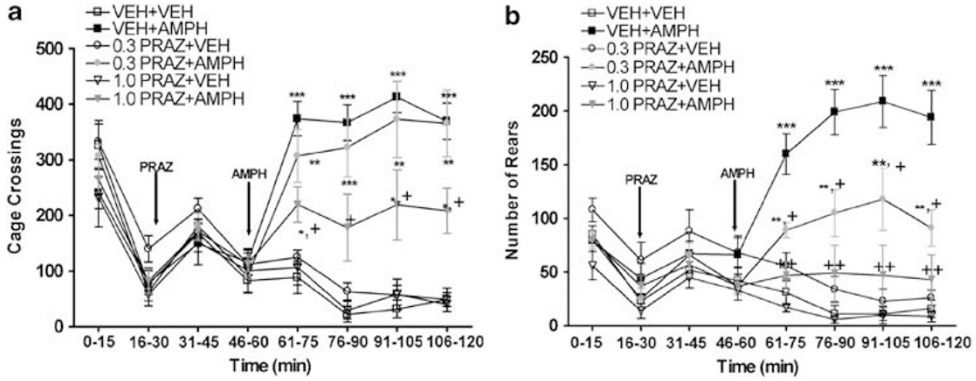

Figure 3 Effects of pretreatment with the α1 receptor antagonist, prazosin (PRAZ), on amphetamine (AMPH)-induced locomotion (a) and rearing (b). Values represent means ± SEM for each drug condition. Doses are in mg/kg. Arrows indicate the timepoint in the test session at which drugs were administered. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ relative to VEH + VEH condition; $^{+}P<0.05$, $^{++}P<0.01$, relative to VEH + AMPH condition.

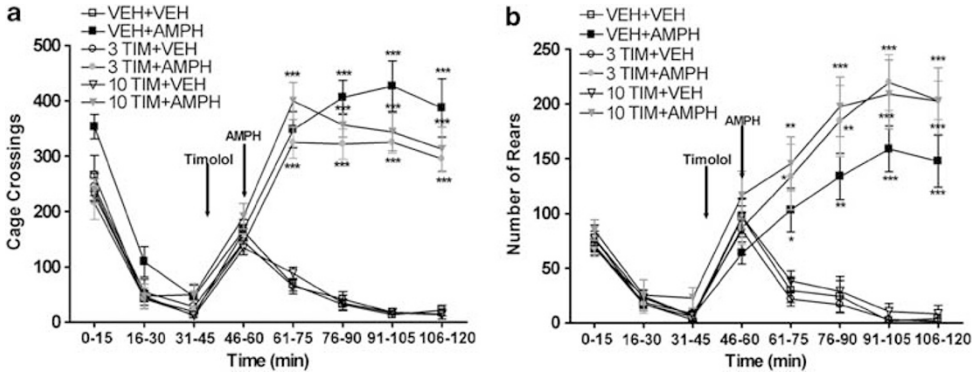

Figure 4 Effects of pretreatment with the β receptor antagonist, timolol (TIM), on amphetamine (AMPH)-induced locomotion (a) and rearing (b). Values represent means ± SEM for each drug condition. Doses are in mg/kg. Arrows indicate the timepoint in the test session at which drugs were administered. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ relative to VEH + VEH condition.

pretreatment and AMPH treatment ($F(2,42)=1.5$, NS). There was a main effect of time ($F(3,126)=4.6$, $P<0.005$) and a significant interaction between time and AMPH treatment ($F(3,126)=21.1$, $P<0.001$). There was no significant interaction between time and timolol pretreatment ($F(6,126)=0.4$, NS) and no significant three-way interaction between time, pretreatment, and treatment ($F(6,126)=0.2$, NS). *Post hoc* tests showed that all AMPH-treated groups had significantly higher rearing values than the VEH + VEH group, at every post-AMPH timepoint ($P<0.05$–$P<0.001$). Thus, timolol did not reduce AMPH-induced increases in rearing.

Experiment 5: Intra-Accumbens Terazosin Reverses AMPH-Induced PPI Deficits

As in previous experiments, there was a main effect of AMPH treatment on PPI ($F(1,11)=7.82$, $P<0.017$), with AMPH treatment producing a robust decrease in PPI at all three prepulse intensities ($P<0.01$) (Figure 5a). There was no main effect of terazosin pretreatment on PPI ($F(1,11)=0.9$, NS), however, there was a significant interaction between terazosin pretreatment and AMPH treatment ($F(1,22)=9.2$, $P<0.012$). Subsequent *post hoc* tests showed that PPI levels at the 3-dB and 9-dB prepulse intensities were significantly higher ($P<0.05$) for the terazosin + AMPH condition, compared with PPI levels for the vehicle + AMPH condition; terazosin + AMPH values did not differ significantly from vehicle + vehicle values (Figure 5). Injector placements for this experiment are shown in Figure 6. These results indicate that antagonism of α1 NE receptors in NAccSh significantly reduced the deficit in PPI caused by systemic AMPH. As with the previous experiments, this normalization of PPI deficits was independent of alterations in startle magnitude, because the reduction in startle magnitude that was caused by AMPH (main effect of treatment ($F(1,11)=43.3$, $P<0.001$)) was not changed by intra-NAccSh terazosin (no significant main effect of terazosin ($F(1,11)=0.5$, NS) nor a terazosin X AMPH interaction ($F(1,11)=0.1$, NS)). Thus, regardless of drug infusion into NAccSh, AMPH-induced startle values were significantly lower than those for the vehicle + vehicle condition ($P<0.01$).

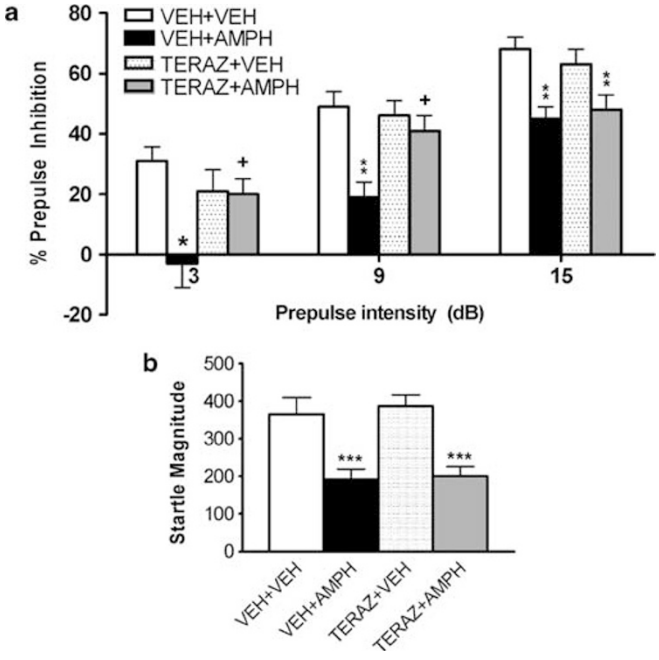

Figure 5 Effects of intra-nucleus accumbens shell (NAccSh) infusion of the α1 receptor antagonist, terazosin (TERAZ), on (a) prepulse inhibition and (b) startle magnitude after systemic amphetamine (AMPH) administration. Values represent means ± SEM for each drug condition. Prepulse intensity indicates decibels above the background noise level. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, relative to VEH + VEH condition; $^{+}P<0.05$ relative to VEH + AMPH condition.

DISCUSSION

This study tested the hypothesis that indirect stimulation of postsynaptic NE receptors contributes to AMPH-induced deficits in PPI. Consistent with many previous reports, AMPH disrupted PPI and increased exploratory behaviors (locomotion and rearing) (Blanc *et al*, 1994; Dickinson *et al*, 1988; Mansbach *et al*, 1988; Ott and Mandel, 1995; Swerdlow *et al*, 1990, 2003). Both the α1 receptor antagonist, prazosin, and the β receptor antagonist, timolol, blocked deficits in PPI induced by AMPH, indicating that α1 and β NE receptors are necessary for AMPH-induced deficits in PPI.

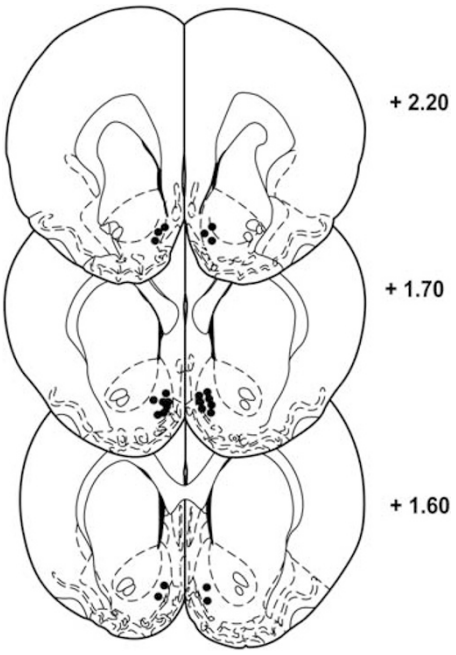

Figure 6 Injector tip locations within the nucleus accumbens shell for rats in experiment 5. Numbers are mm from bregma.

Prazosin also attenuated AMPH-induced increases in locomotion and rearing. Taken together, these data indicate that postsynaptic NE receptor activation, particularly at $\alpha 1$ receptors, underlies two classic behavioral features of AMPH administration: disruption of sensorimotor gating and hyperactivity. The present findings also for the first time indicate that the NAccSh may be an anatomical substrate through which increased NE transmission might mediate AMPH-induced PPI deficits, as intra-shell infusion of the $\alpha 1$ receptor antagonist terazosin also prevented PPI deficits arising from systemic AMPH administration. Thus, indirect stimulation of $\alpha 1$ and β NE receptors by AMPH because of its enhancement of NE transmission (Florin *et al*, 1994; Kuczenski and Segal, 1992; Robertson *et al*, 2009) leads to a reduction in sensorimotor gating. Interestingly, the failure of the high doses of prazosin and timolol to reverse AMPH-induced PPI deficits could be due to the tendency of these doses to reduce PPI on their own, and may reflect the existence of an optimal range of postsynaptic NE transmission that supports PPI, with either reductions or elevations from this equilibrium resulting in decreased PPI levels.

AMPH-induced decreases in startle magnitude were not affected by either prazosin or timolol in spite of the potent reversal of AMPH-induced PPI deficits by these drugs, suggesting that these NE receptor-mediated effects of AMPH on PPI cannot be accounted for by simple nonspecific changes in startle magnitude. Direct stimulation of postsynaptic NE receptors also disrupts PPI in a manner that is dissociable from changes in startle reactivity (Alsene *et al*, 2006). There similarly was a dissociation between the effects of NE receptor antagonists on AMPH-induced deficits in PPI and hyperactivity, suggesting that the mechanisms subserving these two well-documented behavioral sequelae of AMPH may differ. Prazosin, but not timolol, blocked AMPH-induced increases in locomotion and rearing, suggesting that indirect stimulation of $\alpha 1$, but not β receptors, contributes to AMPH-induced hyperactivity under the current experimental conditions. These findings agree with earlier studies (Blanc *et al*, 1994; Colussi-Mas *et al*, 2005; Dickinson *et al*, 1988; Drouin *et al*, 2002a, b). The same doses of timolol that were ineffective in blocking AMPH-induced hyperactivity did potently reverse AMPH-induced PPI deficits in these studies, which is consistent with previous indications that these doses of timolol are behaviorally active (Colussi-Mas *et al*, 2005). Thus, both $\alpha 1$ and β receptors contribute to the PPI-disruptive effects of AMPH, but the locomotor activity-enhancing effects of AMPH appear to be more reliant on $\alpha 1$ receptors. This dissociation could result from the differing anatomical distributions of $\alpha 1$ and β receptors (Nicholas *et al*, 1996; Pupo and Minneman, 2001); for example, it is possible that there may be a set of distinct sites that support β receptor-mediated disruptions of PPI but not hyperactivity.

The present finding that antagonism of $\alpha 1$ receptors within the NAccSh markedly reduced PPI deficits after systemic AMPH administration suggests that indirect stimulation of accumbens-localized $\alpha 1$ receptors is one central anatomical substrate through which AMPH decreases sensorimotor gating. This site is innervated heavily by NE-synthesizing neuron terminals, and nucleus accumbens NE efflux increases five- to sevenfold after systemic AMPH administration (Berridge *et al*, 1997; Delfs *et al*, 1998; McKittrick and Abercrombie, 2007). Furthermore, AMPH-induced hyperactivity is reduced by antagonism of $\alpha 1$ NE receptors in prefrontal cortex (PFC) (Darracq *et al*, 1998). Given that PFC is known to modulate PPI (Lacroix *et al*, 2000; Shoemaker *et al*, 2005), it would be of interest in future studies to determine if, similar to the present finding with the NAccSh, blockade of $\alpha 1$ receptors in PFC would also reduce AMPH-induced PPI deficits. In addition, immunohistochemical and autoradiographic studies indicate the presence of $\alpha 2$ and β NE receptors within the nucleus accumbens (Carvalho *et al*, 2010; Ma *et al*, 2006; Palacios and Kuhar, 1982). Given that the present AMPH-induced PPI deficits were also blocked by systemic timolol (a β receptor antagonist), it also would be of interest to determine if antagonism of these other receptors in accumbens similarly blocks these PPI deficits.

Although it has been known for many years that NE regulates attention, arousal, memory, and cognition, its role in sensorimotor gating has not been well studied (Aston-Jones and Cohen, 2005; Berridge, 2008; Robbins and Arnsten, 2009). Given the presence of PPI deficits in several psychiatric illnesses in which putative NE system dysfunction is hypothesized (Braff *et al*, 2001b), it is reasonable to predict that alterations in NE transmission could underlie PPI deficits in these illnesses. Genetically altered mice lacking $\alpha 2A$ or $\alpha 2C$ receptors show a disruption of basal PPI and an enhancement of AMPH-induced PPI deficits because of increased NE transmission centrally (resulting from removal of autoreceptor-mediated inhibition over NE synthesis and release) (Lahdesmaki *et al*, 2002, 2004; Sallinen *et al*, 1998). Thus, it is somewhat surprising that systemic clonidine, an agonist for $\alpha 2$ receptors, failed to reverse AMPH-induced PPI deficits in a recent study (Swerdlow *et al*, 2006). Yet, the dose of AMPH that was

used in that study (4.5 mg/kg) was much higher than that of this study; when lower doses of AMPH are given, clonidine does antagonize AMPH-induced behavioral effects (Vanderschuren *et al*, 2003). It would be interesting to determine whether PPI deficits produced by low doses of AMPH can be blocked by clonidine. Regardless, the present findings clearly indicate that blockade of postsynaptic α1 and β NE receptors prevents PPI deficits induced by AMPH, which is in agreement with previous reports that stimulation of postsynaptic NE receptors disrupts PPI (Alsene *et al*, 2006; Carasso *et al*, 1998). Importantly, for the first time a specific neuroanatomical substrate, the NAccSh, has been implicated in this effect.

There is reason to believe that NE regulation of PPI may vary across anatomical subregions of the nucleus accumbens, as has been observed with other systems (Caine *et al*, 2001; Hara and Pickel, 2008; Kodsi and Swerdlow, 1997; Pothuizen *et al*, 2005; Swerdlow *et al*, 2001; Wan *et al*, 1994). After systemic AMPH administration, NE release is greater in accumbens shell *vs* core (McKittrick and Abercrombie, 2007). Coupled with the finding that accumbens lacks α2 autoreceptor-mediated inhibition of NE (Schoffelmeer *et al*, 1998), one might expect that AMPH-induced NE release within shell would not be mitigated by the normal opposing influence on NE transmission of autoregulatory shut-off mechanisms, resulting in markedly elevated levels of NE in this site available to stimulate postsynaptic NE receptors. Our lab has found that direct stimulation of α1 and β adrenoceptors in accumbens shell, but not core, disrupts PPI (Alsene *et al*, 2007), thus the present finding that blocking α1 receptors within accumbens shell reverses AMPH-induced PPI deficits is consistent with this mechanism.

The present findings add to the growing consensus that certain behavioral effects of AMPH that previously were attributed primarily to increases in DA transmission in fact are mediated also in part by NE (Berridge and Morris, 2000; Blanc *et al*, 1994; Dickinson *et al*, 1988; Drouin *et al*, 2002a). A complex set of site- and receptor-dependent interactions between DA and NE systems contribute to other behavioral effects of AMPH (Darracq *et al*, 1998; Drouin *et al*, 2002a, b; Espejo and Minano, 2001; Pascucci *et al*, 2007; Tassin, 1998; Vanderschuren *et al*, 1999, 2003; Villegier *et al*, 2003). Whether or not similar dynamics regulate PPI remains to be determined, as there also is evidence for independent actions of each system on PPI (Bakshi and Geyer, 1997; Carasso *et al*, 1998; Swerdlow *et al*, 2006). Thus, the nature of potential DA–NE interactions in PPI remains to be defined further; nevertheless, the present results indicate a prominent role for α1 NE receptors in accumbens shell in the PPI-disruptive effects of AMPH.

It has been argued that actions at NE receptors may contribute to the unique effects of second-generation antipsychotics (Bakshi and Geyer, 1997; Baldessarini *et al*, 1992; Breier, 1994; Svensson, 2003), but clinically, the question of whether NE receptor-based medications are effective antipsychotics has not been well examined. There is some evidence for enhancement of antipsychotic function by compounds that reduce central NE transmission or block postsynaptic NE receptors, suggesting the possibility of NE-based therapeutics as adjunct treatments for schizophrenia, but there are also examples of no clinical improvement with these compounds in schizophrenia (Berlant, 1987; Freedman *et al*, 1982, 2001; Maas *et al*, 1995; Wahlbeck *et al*, 2000).

Perhaps less controversial is the notion that drugs that modify central NE transmission have clinical utility in the treatment of several other psychiatric illnesses in which cognitive NE-based dysfunction is hypothesized (Arnsten *et al*, 2007; Bhidayasiri, 2005; Boehnlein and Kinzie, 2007). Among these conditions are attention deficit disorder, Tourette's syndrome, and post-traumatic stress disorder, all of which have been associated with deficient PPI (Braff *et al*, 2001b). Thus, NE-based PPI deficits may provide a good model for a separate subset of affected individuals (Alsene *et al*, 2006; Swerdlow *et al*, 2006). The present results provide an important new insight into the pathways that may be involved in these deficits by showing that within the NAccSh, enhanced NE transmission may underlie the PPI-disruptive effects of AMPH. Indeed, as subsequent studies systematically will delineate the specific circuits mediating NE-based PPI deficits, novel DA-independent substrates of sensorimotor gating abnormalities may emerge and shed further insight into the deficits that are manifest clinically. As these studies underscore, postsynaptic NE receptors do have a significant role in the PPI-disruptive effects of AMPH, which is one of the most widely used pharmacological models of deficient sensorimotor gating, thus these findings provide a solid foundation for future investigation into novel systems that regulate this important form of information processing.

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DISCLOSURE

Dr Bakshi has no conflicts to report. Dr Alsene was a graduate student in Dr Bakshi's laboratory during the time when the studies in this paper were completed, and while the paper was written, thus has no conflicts to report. At the present time, Dr Alsene is a full-time employee (Medical Writer) with Covance, which has no relationship to the present work. At no time during the course of the studies described in this paper was any author receiving any materials or compensation from any outside company.

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