



Published in final edited form as:

*Behav Brain Res.* 2014 April 15; 263: 80–89. doi:10.1016/j.bbr.2014.01.032.

## Time-Dependent Effects of Prazosin on the Development of Methamphetamine Conditioned Hyperactivity and Context-Specific Sensitization in Mice

André O. White<sup>1,2</sup> and Anthony S. Rauhut<sup>1</sup>

<sup>1</sup>Dickinson College

### Abstract

The present experiments examined the effects of prazosin, a selective  $\alpha_1$ -adrenergic receptor antagonist, on the development of methamphetamine conditioned hyperactivity and context-specific sensitization. Mice received an injection of vehicle (distilled water) or prazosin (0.5, 1.0 or 2.0 mg/kg) 30 minutes *prior* to a second injection of vehicle (saline) or methamphetamine (1.0 mg/kg) during the conditioning sessions (Experiment 1). Following the conditioning sessions, mice were tested for conditioned hyperactivity and then tested for context-specific sensitization. In subsequent experiments, mice received an injection of vehicle (distilled water) or prazosin (2.0 mg/kg) immediately (Experiment 2) or 24 hours (Experiment 3) *after* the conditioning sessions and then tested for conditioned hyperactivity and context-specific sensitization. Prazosin dose-dependently blocked the development of methamphetamine conditioned hyperactivity and context-specific sensitization when administered prior to the methamphetamine during the conditioning phase; however nonspecific motor impairments also were observed (Experiment 1). Immediate (Experiment 2), but not the 24-hour delay (Experiment 3), post-session administration of prazosin attenuated the development of methamphetamine conditioned hyperactivity and context-specific sensitization. Nonspecific motor impairments were not observed in these latter experiments. Collectively, these results suggest that the  $\alpha_1$ -adrenergic receptor mediates the development of methamphetamine-conditioned hyperactivity and context-specific sensitization, perhaps by altering memory consolidation and/or reconsolidation processes.

### Keywords

psychostimulants; methamphetamine;  $\alpha_1$ -adrenergic receptor; antagonist; memory consolidation; memory reconsolidation; prazosin; locomotor activity; conditioning; sensitization

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**Corresponding Author:** Anthony S. Rauhut, PhD. Department of Psychology Kaufman Hall Dickinson College Carlisle, PA 17013, USA Phone: (717) 245-1079 Fax: (717)245-1971 rauhuta@dickinson.edu.

André O. White (aowhite@uci.edu)

<sup>2</sup>*Present Address:* University of California, Irvine, 301 Qureshey Research Lab, Mail Code: 3800, Irvine, CA 92697

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## 1. Introduction

In rodents, repeated administration of amphetamine or methamphetamine results in a robust increase in locomotor activity, a phenomenon known as *behavioral sensitization* (see [1] for a review). In the typical behavioral sensitization paradigm, some rodents receive daily pairings of amphetamine in the locomotor activity chambers (i.e., paired rodents) while other rodents receive comparable amphetamine exposures in their home cages (i.e., unpaired rodents). At some later point in time (test session), all rodents are “challenged” with amphetamine while in the locomotor activity chambers and paired rodents will show an enhanced response (i.e., greater locomotor activity, *context-specific sensitization*) compared to unpaired rodents (*context nonspecific sensitization*). Behavioral sensitization reflects both the pharmacological action of the drug (i.e., the unconditioned drug effect) as well as non-pharmacological, associative learning processes (i.e., classical conditioning; see [2] for a discussion of the role of classical conditioning in behavioral sensitization). That is, with respect to the latter, after the repeated pairings of the locomotor activity chamber (conditioned stimulus - CS) with the locomotor-activating effects of the drug (e.g., methamphetamine; unconditioned stimulus - US), the chamber itself will elicit an increase in locomotor activity (i.e., a conditioned hyperactive response; conditioned response - CR) relative to a control group. Moreover, the enhanced pharmacological response observed in paired rodents when challenged with amphetamine on the test session compared to unpaired rodents demonstrates context-specific sensitization (see [3] for a recent demonstration of methamphetamine conditioned hyperactivity and context-specific sensitization) and also thought to reflect the contribution of associative learning processes [4, 5].

The mesolimbic dopaminergic system has been implicated in the development of amphetamine-produced context-specific sensitization and conditioned hyperactivity (see [6] for a review). Studies, employing a number of techniques, have supported this role. For example, neurochemical studies have shown that 6-hydroxydopamine lesions of the nucleus accumbens attenuate the development of the conditioned hyperactive response to amphetamine [7] and concentrations of a metabolite of dopamine, homovanilic acid, are higher in mesolimbic and caudate regions of the brain in conditioned compared to pseudo-conditioned rats [8]. Pharmacological studies have shown that selective dopaminergic subtype-1 or -2 (D<sub>1</sub> or D<sub>2</sub>) receptor antagonists attenuate and/or block the development of conditioned hyperactivity to amphetamine, supporting a role of these receptor subtypes in the development of the response [9, 10]. The role of the D<sub>1</sub>-dopamine receptor is further supported by studies employing genetic manipulations (e.g., gene knockout). For example, D<sub>1</sub>-dopaminergic receptor knockout mice show enhanced context-specific sensitization and conditioned hyperactivity following repeated context-amphetamine pairings [11]. Finally, it has been shown that the partial D<sub>3</sub>-dopaminergic receptor agonist, BP 897, attenuates the expression, but not the development, of amphetamine-produced conditioned hyperactivity when injected systemically [12] into the basolateral amygdala or nucleus accumbens [13]. Collectively, these latter studies suggest that dopaminergic receptors differentially mediate the development of amphetamine-produced conditioned hyperactivity.

Recently, studies have shown that the noradrenergic system interacts with the mesocorticolimbic dopaminergic system, via the  $\alpha_1$ -adrenergic receptor, to modulate

dopaminergic activity as well as the sensitizing (pharmacological) and conditioned rewarding effects of drugs of abuse (see [14] for a review). Neuroanatomical studies have shown that noradrenergic neurons, arising from the locus coeruleus, A<sub>1</sub> and A<sub>2</sub> nuclei, have excitatory projections to dopaminergic-containing neurons in the ventral tegmental area [15]. Furthermore, neurons that release norepinephrine project to and stimulate, through the  $\alpha_1$ -adrenergic receptor, neurons that release dopamine, leading to increased D<sub>1</sub>- and D<sub>2</sub>-dopaminergic receptor activity downstream [16]. Electrophysiological studies have shown that stimulation of  $\alpha_1$ -adrenergic receptors, typically from the locus coeruleus, directly increases the likelihood of action potentials in both the ventral tegmental area and substantia nigra pars compacta [17]. Conversely, antagonism of the  $\alpha_1$ -adrenergic receptors with the selective  $\alpha_1$ -adrenergic receptor antagonist, prazosin, inhibits bursts firing of ventral tegmental dopaminergic neurons [18]. The locus coeruleus also has dense projections to the prefrontal cortex, sending excitatory glutamatergic projections to the ventral tegmental area dopaminergic neurons [19, 20], and this projection is critical for dopamine release in the nucleus accumbens, as lesions of norepinephrine-containing prefrontal cortical neurons abolishes amphetamine-induced dopamine release [21]. Moreover, site-specific infusion of prazosin into prefrontal cortical neurons blocks release of dopamine into the nucleus accumbens, indicating that the  $\alpha_1$ -adrenergic receptor mediates this effect [22, 23]. With respect to amphetamine, behavioral studies further corroborate an interaction of the noradrenergic and dopaminergic systems via the  $\alpha_1$ -adrenergic receptor. For example, lesions of the locus coeruleus attenuate amphetamine-induced locomotor activity [24] and prazosin attenuates amphetamine-induced hyperactivity [23, 25]. Studies have shown that depletion of norepinephrine in the medial prefrontal cortex attenuates amphetamine-produced conditioned place preference and amphetamine-induced mesoaccumbens dopamine release in mice [21]. Finally,  $\alpha_{1b}$ -adrenergic receptor knockout mice are less sensitive to the locomotor-activating effects of amphetamine [26]. Collectively, these studies suggest that the noradrenergic system interacts with the dopaminergic system, via the  $\alpha_1$ -adrenergic receptor, to mediate the locomotor-activating and conditioned rewarding properties of amphetamine.

To date, no research has examined the interaction of the noradrenergic and dopaminergic systems in mediating the pharmacological or conditioned components of methamphetamine sensitization, particularly focusing on the  $\alpha_1$ -adrenergic receptor. Thus, in Experiment 1, prazosin was administered at various doses (0.5, 1.0 or 2.0 mg/kg) 30 minute (min) prior to mice receiving a dose of methamphetamine (1.0 mg/kg). Then, the mice were placed in a locomotor activity chamber for a 30-min conditioning session and their locomotor activity recorded. This experiment found that when the highest prazosin dose (2.0 mg/kg) was administered 30 min prior to the methamphetamine, then the development of conditioned hyperactivity and context-specific sensitization was attenuated. However, because the prazosin was administered *prior* to the conditioning event, this experiment failed to specify whether the prazosin disrupted the development of the conditioned hyperactive response and context-specific sensitization by altering acquisition processes (i.e., learning at the time of conditioning event) or consolidation processes (e.g., memory formation after the conditioning event). Research has shown that memory consolidation is temporally limited [27]. That is, after the conditioning event, the memory trace is malleable and susceptible to

pharmacological manipulations during an experimenter-defined window of time (< less 24 hours, h). For example, previous research has found that immediate, but not delayed (24 h), administration of lidocaine into the amygdala, following the conditioning event, impaired recall on an inhibitory avoidance task [28]. Thus, in order to determine whether prazosin disrupted the development of methamphetamine conditioned hyperactivity and context-specific sensitization, Experiments 2 and 3 examined the effect of *immediate* (Experiment 2) vs. *delayed* (24 h; Experiment 3) post-session administration of prazosin on the development of methamphetamine conditioned hyperactivity and context-specific sensitization. If prazosin disrupts the development of conditioned hyperactivity and context-specific sensitization by altering memory consolidation processes, then the immediate, but not delayed, post-session administration of prazosin should disrupt the development of conditioned hyperactivity and context-specific sensitization.

## Materials and Methods

### 1.1. Subjects

Male, adolescent Swiss-Webster mice ( $N = 160$ ) were obtained from Charles River Laboratories (Raleigh, N.C). Mice were 25-27 days of age at the time of arrival and were 42-44 days of age at the time of testing. Mice were group-housed (four per tub) in a ventilated-caging system (Vent-Air, PA) lined with paper bedding (Care-free Ultra). Food (Purina Fortified Rodent Chow) and water were made available *ad libitum*. The room was kept at ~ 21 degrees (Celsius) and the lights cycled on a 12:12 light/dark cycle in which the light turned on at 0900 h. All mice were handled for 1 min each day for a week prior to the start of the experiments (acclimation period). The tails of the mice were marked for identification. The average weight of the mice at the start of the 10-day experiments was approximately 30 g. The experiments conform to the guidelines established by the NIH Guide for the Care and Use of Laboratory Animals (2011 Edition) and the APA Ethical Principles of Psychologists and Code of Conduct. The Institutional Animal Care and Use Committee at Dickinson College approved the experiments described.

### 1.2. Drugs

All drugs were obtained from Sigma (St. Louis, MO). Methamphetamine HCl was dissolved into physiological saline (0.9% vehicle). The methamphetamine was injected subcutaneously (s.c.) at 1.0 mg/kg (body weight) in a volume of 10 ml/kg. Prazosin was dissolved in distilled water. Prazosin was injected intraperitoneally (i.p.) in a volume of 2 ml/kg. All drug doses are expressed as the weight of their salts.

### 1.3. Apparatus

Eight, open-field chambers (MED-OFA-510; Med-associates, VT) were used for all locomotor activity sessions. Each chamber was placed in a sound-attenuated cubicle (MED-OFA-022, Med-Associates, Burlington, VT) containing a fan and lights. The walls of the activity chambers were made of Plexiglas with the interior dimensions measuring 27.9 cm x 27.9 cm. Locomotor activity, defined as distance traveled (cm), was determined by three, 16-beam I/R arrays (X, Y and Z axes) and photo beam breaks were recorded by a personal computer (Activity Monitor software; Med-associates, VT) located in the same room as the

chambers. The chambers were cleaned with a disinfectant solution (Precise QTB/Caltech, Midland, MI) following each 30 min locomotor-activity session. A small, cap-size amount of anise extract (McCormick, Hunt Valley, MD) was used daily to scent each open-field chamber and provide an olfactory cue.

#### 1.4. Procedure

The methamphetamine dose and conditioning procedure chosen were similar to those previously found to produce robust conditioned hyperactivity and context-specific sensitization in mice [3]. Following the acclimation period, the experiments consisted of 2 phases: conditioning and tests. The conditioning phase consisted of 4 alternating chamber and home-cage days. On chamber days (1, 3, 5 and 7), paired mice ( $n = 14/\text{group}$ ) received an injection (i.p.) of vehicle (distilled water) or prazosin (0.5 – 2.0 mg/kg; Experiment 1) 30 min *prior* to receiving methamphetamine (1.0 mg/kg) and then placed in the locomotor activity chamber for a 30-min period. On chamber days, unpaired mice ( $n = 14/\text{group}$ ) received vehicle or prazosin (0.5 – 2.0 mg/kg) followed 30 min later by an injection of vehicle and placed in the locomotor activity chamber for a 30-minute period. The prazosin doses and injection parameters were based on a previous study [29]. In Experiments 2 and 3, paired and unpaired mice ( $n = 6/\text{group}$ ) received either prazosin (2.0 mg/kg) or vehicle immediately or 24 h *after* the conditioning sessions, respectively, on chamber days. On the 4 intervening home-cage days (2, 4, 6, and 8), paired mice received an injection of vehicle whereas unpaired mice received an injection of methamphetamine in their home cages. In the case of Experiment 3 in which the injection of either prazosin or vehicle occurred on home-cage days by design, the prazosin or vehicle was administered 30 min after the injections of methamphetamine or saline. The mean plasma half-life of prazosin has been shown to be less than 3 h in rodents [30]. Therefore, prazosin should not have been behaviorally active during the subsequent chamber day. Forty-eight h after the last chamber day, all mice were tested for conditioned hyperactivity (Test 1). At this time, all mice were given an injection of vehicle immediately before placement in the activity chamber for a 30-min session. All mice were tested for context-specific sensitization (methamphetamine challenge) the following day (Test Day 2). On this test day, all mice were given an injection of methamphetamine (1 mg/kg) before a 30-min session in the activity chamber. In all experiments, conditioned hyperactivity and context-specific sensitization were assessed by comparing paired and unpaired mice, an approach taken in a previously-reported study from the laboratory [3]. Mice received their respective treatments Monday through Friday. All mice rested on the weekends.

#### 1.5. Data Analysis

Data for each experiment were analyzed using SPSS (version 21.0). The conditioning data were subjected to three-way analyses of variance (ANOVAs) on the within-subjects factor, Chamber Day (1 and 4), and the between-subjects factors of Conditioning (Paired or Unpaired) and Prazosin Dose (Vehicle, 0.5, 1.0, or 2.0 mg/kg). Two-way ANOVAs were performed on the factors of Conditioning and Prazosin Dose for Test Days 1 and 2, separately. Additional time-course analyses were performed as necessary on particular days of the experiment. These analyses involved three-way ANOVAs on the between-subjects factors, Conditioning and Prazosin Dose, and the within-subjects factor, Session Minute.

Significant main effects and/or interactions of interest motivated follow-up *post hoc* contrasts involving Tukey's Honest Significant Difference tests. Unless other noted, all statistical decisions were made at  $\alpha$  set to 0.05.

### 3. Results

#### 3.1. Experiment 1

Experiment 1 employed a 4 (Prazosin Dose) x 2 (Conditioning) factor design whereby mice received an injection of vehicle or prazosin (0.5, 1.0 or 2.0 mg/kg) 30 min prior to an injection of vehicle (unpaired mice) or methamphetamine (paired mice) and then placed in the locomotor activity chambers during the Conditioning Phase. Following the Conditioning Phase, all mice were tested for conditioned hyperactivity (Test Day 1) and context-specific sensitization (Test Day 2) 24 h apart.

Nine mice were eliminated from the experiment for various reasons. With the exception of Paired-2.0 Prazosin, one mouse from each group was eliminated due to computer malfunctions. Furthermore, one mouse died from Group Unpaired-0.5 Prazosin and one mouse from Group Paired-2.0 Prazosin received the wrong experimental treatment. These mice were excluded from the data analysis. Thus, the sample sizes per group were as follows: Paired-Vehicle ( $n = 13$ ), Paired-0.5 Prazosin ( $n = 13$ ), Paired-1.0 Prazosin ( $n = 13$ ), Paired-2.0 Prazosin ( $n = 13$ ), Unpaired-Vehicle ( $n = 13$ ), Unpaired-0.5 Prazosin ( $n = 12$ ), Unpaired-1.0 Prazosin ( $n = 13$ ) and Unpaired-2.0 Prazosin ( $n = 13$ ).

**3.1.1. Conditioning**—The three-way ANOVA revealed significant main effects of Chamber Day,  $F_{(1, 95)} = 55.3$ ,  $P = 0.000$ , Conditioning,  $F_{(1, 95)} = 61.0$ ,  $P = 0.000$ , and Prazosin Dose,  $F_{(3, 95)} = 11.6$ ,  $P = 0.000$ . The Chamber Day x Conditioning,  $F_{(1, 95)} = 35.6$ ,  $P = 0.000$ , as well as Conditioning x Prazosin Dose,  $F_{(3, 95)} = 6.7$ ,  $P = 0.000$ , interactions were significant. The Chamber Day x Conditioning x Prazosin Dose interaction approached statistical significance,  $F_{(3, 95)} = 2.4$ ,  $P = 0.073$ . *Post hoc* contrasts conducted on Chamber Day 1 revealed that paired mice that received the moderate (1.0 mg/kg) and high (2.0 mg/kg) prazosin doses showed less locomotor activity compared to Paired-Vehicle mice ( $P_s = 0.000$ ), suggesting that these prazosin doses blunted the acute locomotor-activating effects of methamphetamine. However, *post hoc* contrasts also revealed that unpaired mice that received the high prazosin dose (2.0 mg/kg) were less active compared to Unpaired-Vehicle mice ( $P = 0.000$ ), suggesting that the high prazosin produced nonspecific locomotor depression (Figure 1A). *Post hoc* contrasts conducted on Chamber Day 4 revealed that paired mice that received the high (2.0 mg/kg) prazosin dose showed less locomotor activity compared to Paired-Vehicle mice ( $P = 0.001$ ), suggesting that the high prazosin dose blunted the locomotor-activating effects of methamphetamine following repeated administration. None of the unpaired mice that received prazosin were less active than the Unpaired-Vehicle mice on Chamber Day 4 ( $P_s > 0.11$ ), suggesting that mice developed tolerance to the initial locomotor-depressing effects of the high prazosin dose (2.0 mg/kg; Figure 1B).

**3.1.2. Test Day 1**—The two-way ANOVA conducted on Test Day 1 revealed a significant main effect of Conditioning,  $F_{(1, 95)} = 34.6$ ,  $P = 0.000$ , as well as a significant Conditioning

x Prazosin Dose interaction,  $F_{(3, 95)} = 3.9, P = 0.01$ . *Post hoc* contrasts revealed that none of the active prazosin doses differed from the vehicle control dose in paired mice. However, when paired mice were compared to their respective unpaired counterparts, it was found that Paired-Vehicle and Paired-0.5 Prazosin differed from their unpaired counterparts ( $P_s = 0.02$ ), suggesting these paired groups displayed conditioned hyperactivity. Furthermore, when Paired-1.0 Prazosin and Paired-2.0 Prazosin were compared to their respective unpaired counterparts, then they did not differ ( $P_s > 0.9$ ), suggesting that these prazosin doses blocked conditioned hyperactivity (Figure 2A). Moreover, time-course analyses, involving a three-way ANOVA (Conditioning x Prazosin Dose x Session Minute) revealed significant main effects of Conditioning and Session Minute ( $F_s > 30, P_s = 0.000$ ) as well as significant Conditioning x Session Minute and Conditioning x Prazosin Dose interactions ( $F_s > 3.9, P_s = 0.01$ ). No other interactions were statistically significant. *Post hoc* contrasts revealed that Paired-2.0 Prazosin mice were less active than Paired-Vehicle mice during Session Minute 10 ( $P = 0.066$ ; Figure 2B), suggesting that this prazosin dose attenuated conditioned hyperactivity. Unpaired-1.0 Prazosin mice were more active than Unpaired-Vehicle mice during Session Minute 25 ( $P = 0.068$ ; Figure 2C). However, no other group differences were detected in unpaired mice on Test Day 1, suggesting that the prazosin-induced attenuation of conditioned hyperactivity in paired mice was not due to motor problems induced by the high prazosin dose (2.0 mg/kg).

**3.1.3. Test Day 2**—The two-way ANOVA conducted on Test Day 2 revealed a significant main effect of Conditioning,  $F_{(1, 95)} = 6.4, P = 0.01$ , as well as a Conditioning x Prazosin Dose interaction that approached statistical significance,  $F_{(3, 95)} = 2.45, P = 0.068$ . Despite a non-significant interaction, several exploratory contrasts were conducted comparing paired mice to their respective unpaired controls. It was found that only Paired-Vehicle differed from its unpaired counterpart ( $P < 0.07$ ), suggesting this paired group displayed context-specific sensitization (Figure 3A). Paired-0.5, Paired-1.0 and Paired-2.0 Prazosin mice did not reliably differ from their respective unpaired counterparts ( $P_s > 0.41$ ), suggesting that these prazosin doses attenuated context-specific sensitization. Moreover, time-course analyses, involving a three-way ANOVA (Conditioning x Prazosin Dose x Session Minute) revealed significant main effects of Conditioning and Session Minute ( $F_s > 6.4, P_s = 0.01$ ) as well as two interactions, Conditioning x Session Minute and Conditioning x Prazosin Dose, that approached statistical significance ( $F_s > 2.4, P_s = 0.067$ ). No other interactions were statistically significant. *Post hoc* contrasts revealed that Paired-2.0 Prazosin mice were less active than Paired-Vehicle mice during Session Minutes 10 and 20 ( $P_s = 0.05$  Figure 3B), suggesting that this prazosin dose attenuated context-specific sensitization. Unpaired mice receiving active prazosin doses did not differ from Unpaired-Vehicle control mice on Test Day 2 ( $P_s > 0.87$ ; Figure 3C), suggesting that the prazosin-induced attenuation of context-specific sensitization in paired mice was not due to motor problems induced by the high prazosin dose (2.0 mg/kg).

## 3.2. Experiment 2

Experiment 2 employed a 2 (Conditioning) x 2 (Prazosin Dose) factor design whereby mice received an injection of vehicle (unpaired mice) or methamphetamine (paired mice) prior to placement in the locomotor activity chambers during the Conditioning Phase similar to

Experiment 1. However, in Experiment 2, paired and unpaired mice received an injection of either vehicle or prazosin (2.0 mg/kg) *immediately* following each conditioning session and then tested for conditioned hyperactivity (Test Day 1) and context-specific sensitization (Test Day 2) after the completion of the Conditioning Phase.

In total, 24 mice were used in the experiment; however one mouse left the testing area during Test Day 1 of the experiment. Thus, this mouse's data were not available on this day and not included in the Test Day 1 analyses; however, this mouse's data were included in all other analyses.

**3.2.1. Conditioning**—The three-way ANOVA revealed significant main effects of Chamber Day,  $F_{(1, 20)} = 5.9, P = 0.025$  and Conditioning,  $F_{(1, 20)} = 73.0, P = 0.000$ . The Chamber Day x Conditioning,  $F_{(1, 20)} = 21.5, P = 0.000$ , as well as the Chamber Day x Prazosin Dose, interactions were significant,  $F_{(1, 20)} = 6.9, P = 0.016$ . The former significant interaction indicates that paired mice were more active than unpaired mice, reflecting a pharmacological effect of the methamphetamine. The Conditioning x Prazosin Dose approached statistical significance,  $F_{(1, 20)} = 3.1, P = 0.095$ . Importantly, a significant Chamber Day x Conditioning x Prazosin Dose interaction was detected,  $F_{(1, 20)} = 5.3, P = 0.033$ . This significant three-way interaction motivated a *post hoc* contrast that found that Paired-Prazosin mice were less active than Paired-Vehicle mice,  $P = 0.056$ , on the last conditioning day (i.e., Chamber Day 4; Figure 4A).

**3.2.2. Test Day 1**—The two-way ANOVA revealed a significant main effect of Conditioning,  $F_{(1, 19)} = 14.9, P = 0.001$ , but no significant main effect of Prazosin Dose,  $F_{(1, 19)} = 1.8, P = 0.19$ . The former result suggests that paired mice were more active than unpaired mice (i.e., conditioned hyperactivity; Figure 4B). The Conditioning x Prazosin Dose interaction was not significant,  $F_{(1, 19)} = 1.2, P = 0.28$ . Furthermore, a *post hoc* contrast, comparing Paired-Prazosin and Paired-Vehicle mice, revealed no significant differences,  $P = 0.31$ , suggesting that immediate post-session administration of prazosin did not alter conditioned hyperactivity. However, as can be seen in Figure 4B, Paired-Prazosin mice were less active than Paired-Vehicle mice. Thus, to further explore group differences not detected during the analysis of the overall 30-min session, a time-course analysis was conducted. The three-way ANOVA, conducted on the time course data, found a significant main effect of Session Minute,  $F_{(5, 95)} = 68.6, P = 0.000$ , Session Minute x Conditioning interaction,  $F_{(5, 95)} = 8.1, P = 0.000$  and Conditioning x Prazosin Dose x Session Minute interaction,  $F_{(5, 95)} = 2.8, P = 0.022$ . No other interactions were statistically significant. *Post hoc* contrasts found that Paired-Prazosin mice were less active than Paired-Vehicle mice during Session Minute 5,  $P = 0.058$ , suggesting that the post-session administration of prazosin attenuated the development of the conditioned hyperactive response. Unpaired-Prazosin and Unpaired-Vehicle mice did not differ during any time point,  $P_s > 0.71$  (Figure 4C).

**3.2.3. Test Day 2**—The two-way ANOVA revealed a significant main effect of Conditioning,  $F_{(1, 20)} = 5.9, P = .025$ , and a marginally non-significant main effect of Prazosin Dose,  $F_{(1, 20)} = 3.5, P = 0.076$ . The former result suggests that the



methamphetamine challenge produced an increase in activity in paired mice more so than unpaired mice. The Conditioning x Prazosin Dose interaction was not significant,  $F_{(1, 20)} = 42, P = 0.52$ , indicating that the prazosin dose did not significantly alter the locomotor activity in the paired mice compared to the unpaired mice. Paired-Prazosin mice tended to be less active than Paired-Vehicle mice; however, this difference was not statistically significant,  $P = 0.31$ , (Figure 5A). To further explore group differences not detected during the analysis of the overall 30-min session, a time-course analysis was conducted. The three-way ANOVA, conducted on the time course data, indicates a significant main effects of Session Minute,  $F_{(5, 100)} = 18.0, P = 0.000$ , and Conditioning,  $F_{(1, 20)} = 5.9, P = 0.025$ . The main effect of Prazosin Dose approached statistical significance,  $F_{(1, 20)} = 3.5, P = 0.076$ . The Session Minute x Conditioning interaction was significant,  $F_{(5, 100)} = 6.7, P = 0.000$ . No other statistically significant interactions were noted. Paired-Prazosin mice were less active compared to Paired-Vehicle mice during Session Minutes 10 ( $P = 0.03$ ) and 15 ( $P = 0.055$ ). Unpaired-Prazosin and Unpaired-Vehicle mice did not differ during any time point,  $P_s > 0.93$  (Figure 5B).

### 3.3. Experiment 3

Experiment 3 was similar to Experiment 2 and employed a 2 (Conditioning) x 2 (Prazosin Dose) factor design; however, in Experiment 3 paired and unpaired mice received an injection of either vehicle or prazosin (2.0 mg/kg) 24 h after each conditioning session and then tested for conditioned hyperactivity (Test Day 1) and context-specific sensitization (Test Day 2) at the completion of the Conditioning Phase.

**3.3.1. Conditioning**—The three-way ANOVA revealed significant main effects of Chamber Day,  $F_{(1, 20)} = 16.0, P = 0.001$ , and Conditioning,  $F_{(1, 20)} = 32.1, P = 0.000$ , as well as a significant Chamber Day x Conditioning interaction,  $F_{(1, 20)} = 13.7, P = 0.001$ . The latter result indicates that paired mice were more active than unpaired mice, reflecting a pharmacological effect of the methamphetamine. The Chamber Day x Prazosin Dose,  $F_{(1, 20)} = .312, P = 0.58$ , Conditioning x Prazosin Dose,  $F_{(1, 20)} = 1.6, P = 0.21$  and Chamber Day x Conditioning x Prazosin dose,  $F_{(1, 20)} = .080, P = 0.78$ , interactions were not significant. The lack of a significant three-way interaction suggests that the prazosin did not alter the pharmacological effects of methamphetamine in paired mice (Figure 6A).

**3.3.2. Test Day 1**—The two-way ANOVA revealed a significant main effect of Conditioning,  $F_{(1, 20)} = 18.5, P = 0.000$ , but no significant main effect of Prazosin Dose,  $F_{(1, 20)} = .016, P = 0.90$ . These results suggest that paired mice were more active than unpaired mice (i.e., conditioned hyperactivity; Figure 6B). A marginally non-significant Conditioning x Prazosin Dose interaction was detected,  $F_{(1, 20)} = 3.1, P = 0.095$ . Furthermore, a *post hoc* contrast, comparing Paired-Prazosin and Paired-Vehicle mice, revealed no reliable differences,  $P = 0.56$ . Collectively, these results suggest that the administration of prazosin 24 h after the conditioning sessions did not alter methamphetamine conditioned hyperactivity.

**3.3.3. Test Day 2**—The two-way ANOVA revealed a significant main effect of Conditioning,  $F_{(1, 20)} = 11.1, P = 0.003$ , but no significant main effect of Prazosin Dose,

$F_{(1, 20)} = 1.6, P = 0.22$ . This result suggests that paired mice were more active than unpaired mice (i.e. context-specific sensitization; Figure 6C). However, a significant Conditioning x Prazosin Dose interaction was observed,  $F_{(1, 20)} = 7.8, P = 0.011$ . A *post hoc* contrast, comparing Unpaired-Prazosin and Unpaired-Vehicle mice, found that groups were not statistically different,  $P = 0.71$ . However, a similarly-conducted *post hoc* contrast revealed that Paired-Prazosin mice were more active than Paired-Vehicle mice,  $P = 0.044$ , suggesting that the Paired-Prazosin mice showed a greater pharmacological response to the methamphetamine compared to the Paired-Vehicle mice.

#### 4. Discussion

While adolescent compared to adult mice have been shown to be less active following either acute [31] or repeated [32] methamphetamine administration, methamphetamine (1.0 mg/kg) enhanced locomotor activity following either acute (Chamber Day 1) or repeated (Chamber Day 4) administration in adolescent Swiss-Webster mice in the present set of experiments. Furthermore, methamphetamine (1.0 mg/kg) produced a robust conditioned hyperactive response in all experiments, replicating previous work in the laboratory [3].

When prazosin was administered 30 min *prior* to the methamphetamine, then prazosin dose-dependently blocked the locomotor-activating effects of methamphetamine, following acute and repeated administration (Experiment 1). These results are similar to other studies that have shown that antagonism of the  $\alpha_1$ -adrenergic receptor blocks the unconditioned, pharmacological effects of amphetamine in rodents [23, 25]. In Experiment 1, we also found that prazosin dose-dependently blocked the development of conditioned hyperactivity and context-specific sensitization in mice. To our knowledge, these latter findings are the first to show that  $\alpha_1$ -adrenergic receptor antagonism blocks the conditioned component of behavioral sensitization. Unfortunately, all prazosin doses initially decreased locomotor activity in unpaired mice, suggesting that these prazosin doses produced nonspecific motor impairments, complicating the interpretation of the disrupting effects of prazosin in paired mice. Furthermore, because prazosin was administered *prior* to the methamphetamine during the conditioning phase, the results did not indicate if prazosin blocked the development of methamphetamine conditioned hyperactivity and context-specific sensitization by disrupting acquisition (i.e., at the time of training) or post-acquisition (i.e., memory consolidation) processes. Thus, in order to address these limitations, two additional experiments (Experiments 2 and 3) were conducted in which prazosin was administered immediately or 24 h *after* the conditioning sessions.

The results of Experiment 2 showed that immediate post-session administration of prazosin attenuated the pharmacological effects of methamphetamine (Chamber Day 4, Figure 4A) and conditioned hyperactivity (Figure 4C). In contrast, the results of Experiment 3 illustrated that when prazosin was administered 24 h after conditioning it had no effects on the pharmacological effects of methamphetamine (Figure 6A) or conditioned hyperactivity (Figure 6B). Collectively, these results suggest that the post-session administration of prazosin disrupted memory consolidation, and not acquisition, processes. Moreover, in Experiments 2 and 3, when prazosin was administered after the conditioning session, a decrease in locomotor activity was not detected in unpaired mice, suggesting that the

memory-disrupting effects of prazosin in paired mice was not due to nonspecific motor impairments. These results are consistent with other recent pharmacological studies examining the role of  $\alpha_1$ -adrenergic receptors in mediating memory consolidation mechanisms and employing different behavioral conditioning paradigms [33]. For example, Bernardi and Lattel (2010) examined if post-session prazosin treatment altered memory consolidation of extinction, as assessed by contextual fear conditioning and cocaine-conditioned place preference paradigms. These authors found that post-session prazosin treatment retarded the rate of contextual fear extinction and reduced the persistence of extinction following reconditioning of cocaine-produced conditioned place preference, suggesting a role for  $\alpha_1$ -adrenergic receptors in mediating memory consolidation.

The results of Experiment 2 and 3, furthermore, showed that immediate, but not delayed, post-session administration of prazosin attenuated context-specific sensitization, consistent with the idea that post-session prazosin administration blunted context-specific sensitization by altering memory consolidation processes. This finding and interpretation is consistent with another recent behavioral study that found that altering memory consolidation processes (specifically memory *reconsolidation*) attenuates context-specific sensitization [34]. Given that Experiments 2 and 3 of the present report involved post-session pharmacological manipulations done in the context of a multiple-session conditioning paradigm (i.e., 4 chamber + methamphetamine pairings), it is perhaps most accurate to suggest that immediate, not delayed, post-session administration of prazosin disrupted memory consolidation *and/or* reconsolidation processes, resulting in an attenuation of conditioned hyperactivity and context-specific sensitization. The two memory processes have been shown to involve different neuronal mechanisms [35]; however, the multiple-session conditioning paradigm used in the present report does not permit us to specify the precise process (consolidation vs. reconsolidation) targeted by the current pharmacological manipulation.

Two limitations of the context-specific sensitization data were noted in the present report. First, the sensitization procedure used in the present experiments lacked a control group that never received methamphetamine prior to the methamphetamine challenge (Test Day 2). While evidence of sensitization was shown by an increase in locomotor activity following repeated administration of methamphetamine in Paired mice during the Conditioning Phase in the present experiments (see Figures 1A, 4A and 6A), a stronger demonstration of sensitization would have compared mice repeatedly-administered methamphetamine to methamphetamine-naïve mice on the methamphetamine challenge day, Test Day 2. However, the present experiments specifically wanted to examine the effects of prazosin on context-specific sensitization and compare those effects to context nonspecific sensitization; therefore, a protocol was adopted to compare paired and unpaired mice, respectively. A similar approach was adopted in a previous study from the laboratory [3]. Second, paradoxically, Paired-Prazosin mice showed a greater sensitized response following methamphetamine administration compared to Paired-Vehicle mice on Test Day 2 of Experiment 3 (see Figure 6C). Moreover, Unpaired-Vehicle mice displayed an uncharacteristically heightened sensitized response to methamphetamine ( $M = \sim 12,000$  cm) on Test Day 2 of Experiment 3 compared to the Unpaired-Vehicle mice's sensitized response

to methamphetamine on Test Day 2 in previous experiments (e.g., Experiment 2 =  $M = \sim 9,000$  cm; see Figure 5A). At present, it is not known the reason for the enhanced sensitized response to methamphetamine in Paired-Prazosin mice compared to Paired-Vehicle mice. An informal inspection of the data suggests that Paired-Prazosin mice sensitized to methamphetamine more so, though not statistically speaking, than Paired-Vehicle mice during the Conditioning Phase (see Figure 6A), perhaps leading to an enhanced sensitized response to methamphetamine on Test Day 2. Indeed, Paired-Prazosin mice also tended to show, though not statistically speaking, a heightened CR compared to Paired-Vehicle mice on Test Day 1 of Experiment 3 (see Figure 6B). Thus, the methamphetamine challenge on Test Day 2 may have unmasked pre-existing group differences.

Recently, authors have suggested that state-dependent learning mechanisms may contribute to drug conditioning and context-specific sensitization [36]. Braga, Dias, Carey and Carrera (2009) suggested that drug USs, particularly dopamine agonists, produce conditioned hyperactive responses that reflect the presence of both internal (drug effects) and external (e.g., smell of the chamber) cues at the time of testing. Moreover, internal drug cues serve as retrieval cues by way of dopaminergic activation. When animals are tested for conditioned hyperactivity in a non-drug state, the weakened CR stems from the absence of internal drug cues, and lack of dopaminergic activation, relative to those present during conditioning. Conversely, when animals are tested for context-specific sensitization, the drug US is present, resulting in dopaminergic activation and aiding as retrieval cues. Such retrieval cues result in a more robust CR relative to that seen during the test for conditioned hyperactivity. By this account, any mismatch between internal and external cues (differences in dopaminergic states) from the Conditioning-to-Testing Phases would produce a weakened CR, as measured either during tests for conditioned hyperactivity or context-specific sensitization. Thus, it could be argued that the results of Experiment 1, results that found that prazosin dose-dependently attenuated conditioned hyperactivity and context-specific sensitization reflect state-dependent learning. That is, prazosin dose-dependently blunted methamphetamine's dopaminergic activity during conditioning. At the time of testing for conditioned hyperactivity, when there was more dopaminergic activity relative to that present during the Conditioning Phase, the internal cue was weakened and the CR was attenuated subsequently. Likewise, the attenuated response observed in prazosin-pretreated mice during the test for context-specific sensitization, resulted from a mismatch between internal and external cues from the Conditioning-to-Testing Phases (differences in dopaminergic states). While this retrieval hypothesis may explain the results of Experiment 1, the results of Experiment 2 seem incapable with this account. Namely, because prazosin was administered immediately *after* the conditioning session, there would not be a mismatch between internal and external cues from the Conditioning-to-Testing Phases and should not weaken conditioned hyperactivity or context-specific sensitization according to the retrieval hypothesis [36]. However, such a weakening was observed in mice treated with prazosin immediately after the conditioning session. Thus, a memory consolidation account seems to be the most parsimonious explanation of the data.

The ability of prazosin to disrupt memory consolidation/reconsolidation may involve an interaction between the dopaminergic and noradrenergic systems. The dopaminergic



treatments (i.e. prazosin) that target consolidation or reconsolidation processes of drug memories, as suggested by other authors [42-44]. Finally, it has been suggested that memory processes, related to associative learning, contribute to drug sensitization [45, 46] and drug addiction [47, 48] in people. In their seminal theoretical paper [46], Robinson and Berridge (1993) suggested that the “behavioral expression of sensitization-related neuroadaptations should be strongly influenced by associative factors” (p. 259). Moreover, Robinson and Berridge (1993) speculated that the “Incentive Sensitization Theory of Addiction predicts that an especially effective pharmacotherapeutic agent would reverse sensitization-related neuroadaptations” (p. 271). The results of the present report suggest that pharmacologically targeting memory consolidation and/or reconsolidation processes may be a novel approach to alter expression of sensitization-related neuroadaptations, thereby blunting the incentive value of drugs and drug-associated stimuli and reducing the likelihood of relapse in addicts.

## Acknowledgments

The authors appreciate the assistance of Margaret Della Vecchia, Neil Devoe and Ee-Rah Sung in conducting the experiments. These experiments were supported by the Department of Psychology, Dickinson College, and grant (DA019866) awarded by USPHS to A. S. Rauhut.

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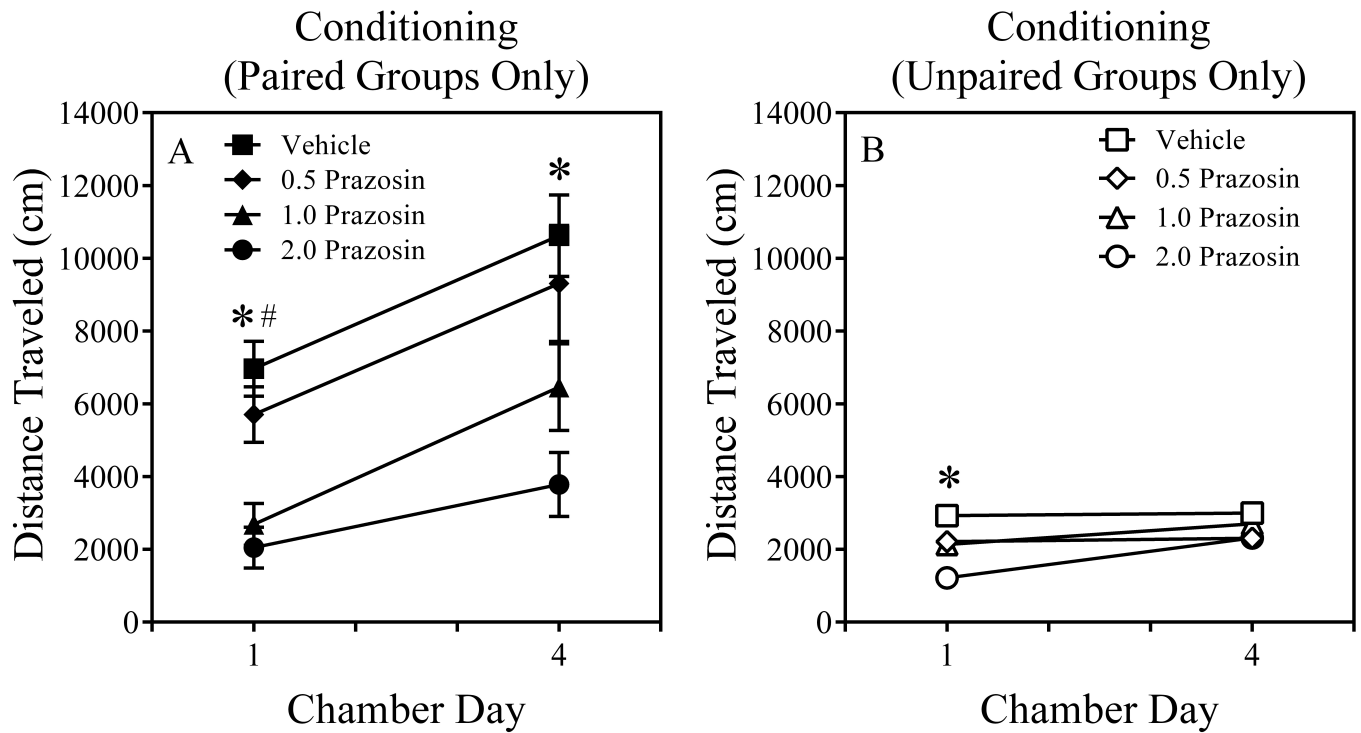
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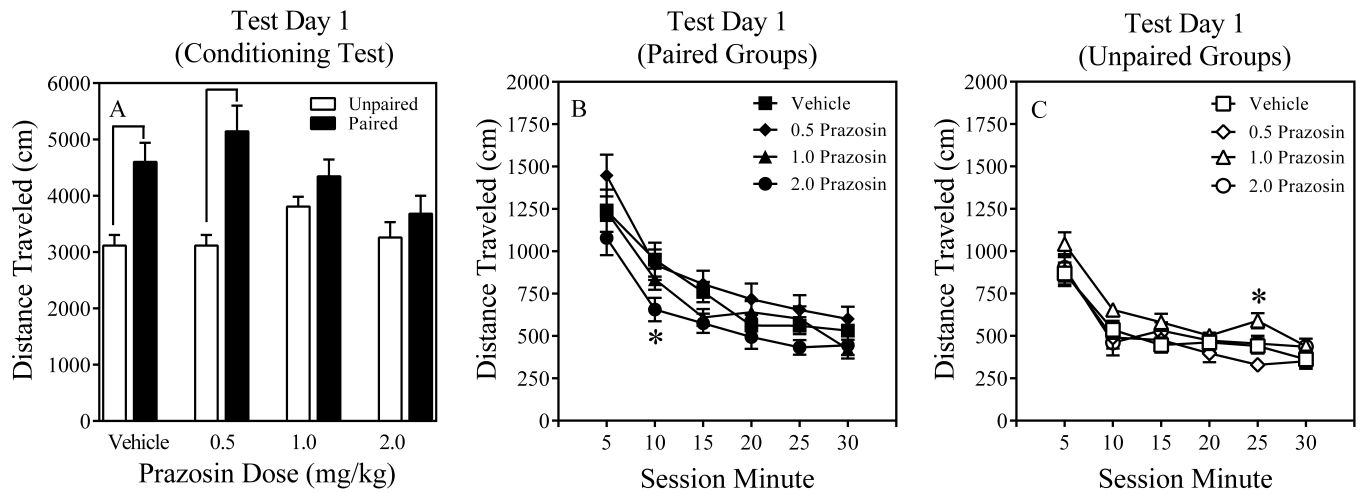
### Highlights

- Examined role of  $\alpha_1$ -adrenergic receptor in conditioned hyperactivity/sensitization
- Pre-session prazosin dose-dependently attenuated locomotor activity nonspecifically
- Immediate post-session prazosin attenuated conditioned hyperactivity/sensitization
- Delayed post-session prazosin did not alter conditioned hyperactivity/sensitization
- Disruption of memory consolidation processes is a possible mechanism of action



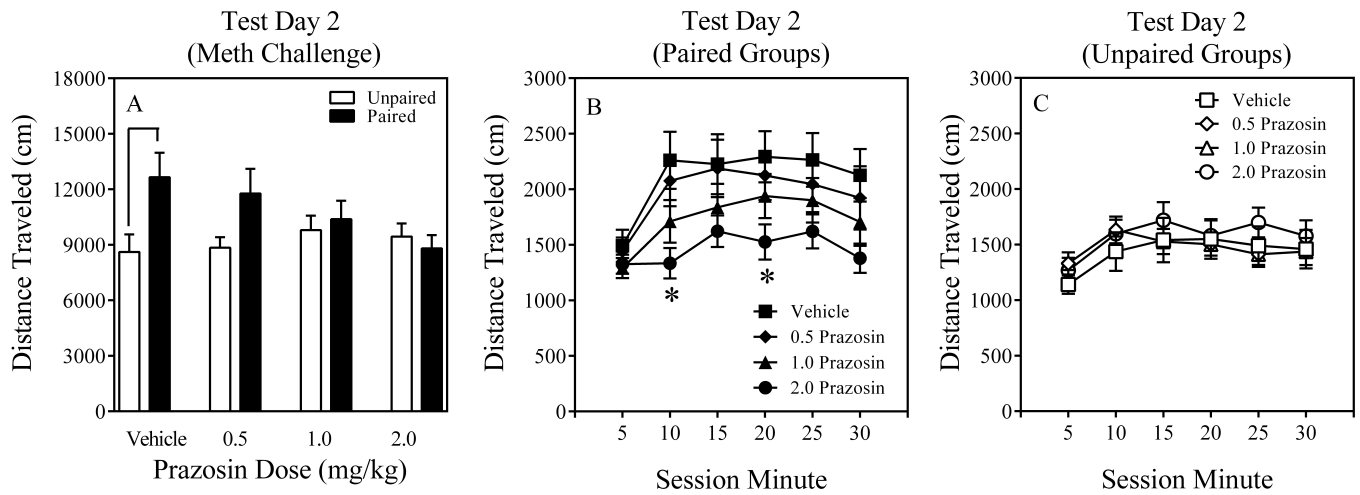
**Figure 1.**

Results of Chamber Days 1 and 4 of the Conditioning Phase for Paired (Panel A) and Unpaired (Panel B) mice of Experiment 1. The error bars represent  $\pm 1$  S.E.M. The pound and asterisk symbols denote a significant difference between 1.0 and 2.0 mg/kg prazosin mice, respectively, and their appropriate vehicle control mice,  $ps < 0.001$ .



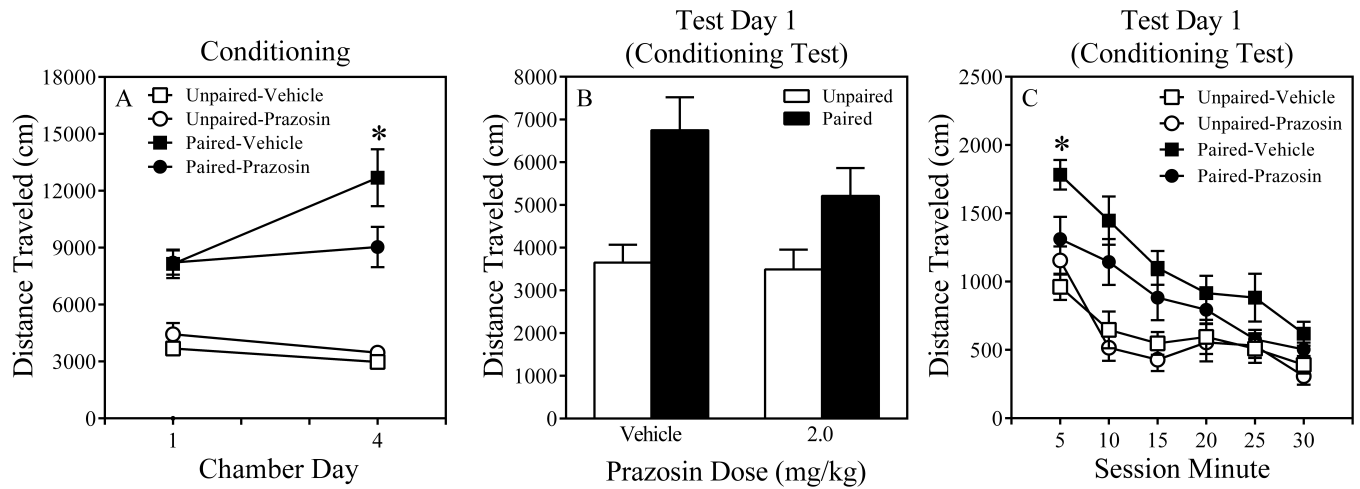
**Figure 2.**

Results of Test Day 1 (Conditioning Test) of Experiment 1 (Panel A). Time course results of Test Day 1 for paired (Panel B) and unpaired (Panel C) mice of Experiment 1. The error bars represent  $\pm 1$  S.E.M. The symbol denotes a significant difference between paired mice and their respective unpaired control mice,  $p_s \leq 0.02$ . The asterisks denote a significant difference between paired or unpaired mice and their respective vehicle control mice at different time points,  $p_s < 0.07$ .

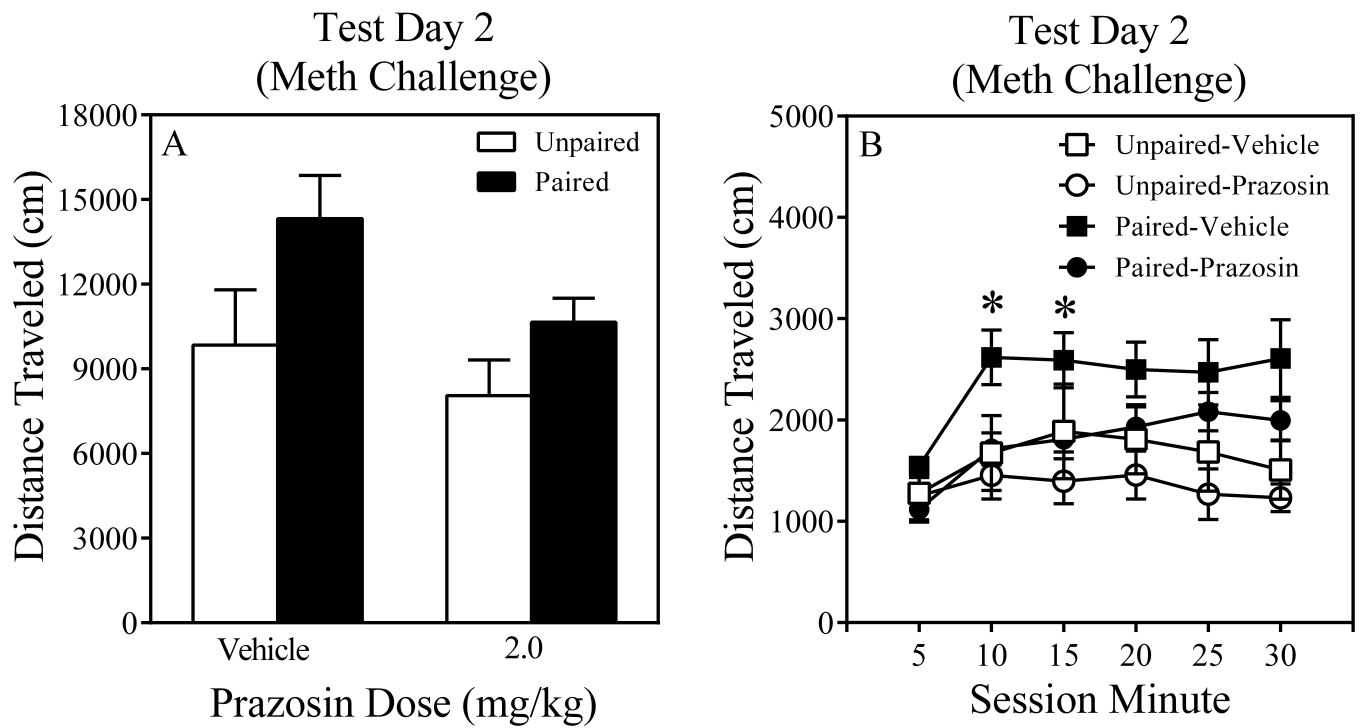


**Figure 3.**

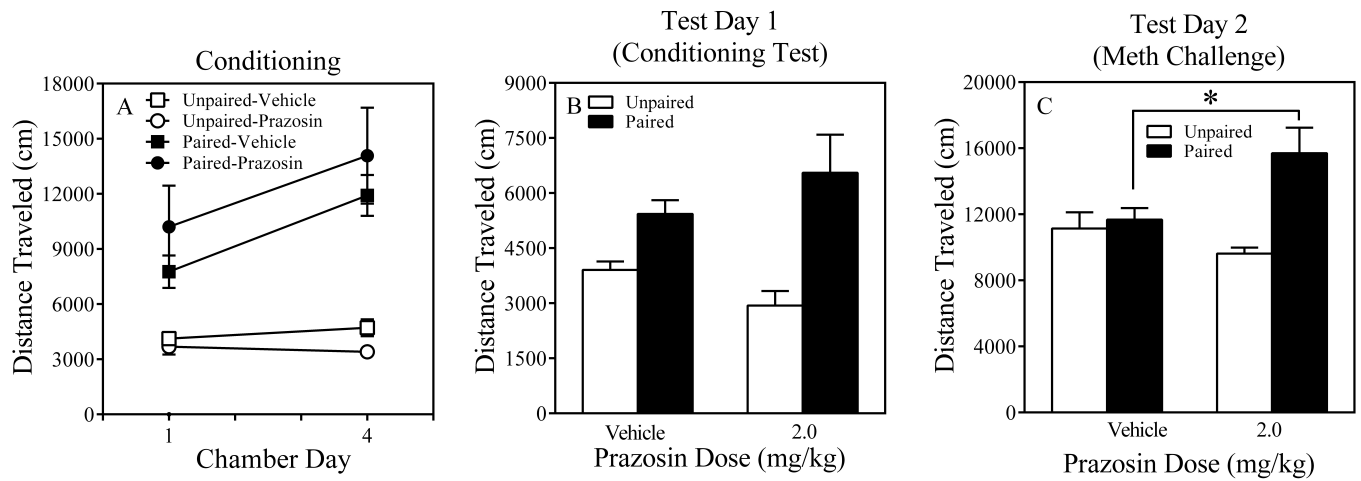
Results of Test Day 2 (Meth Challenge) of Experiment 1 (Panel A). Time course results of Test Day 2 for paired (Panel B) and unpaired (Panel C) mice of Experiment 1. The error bars represent  $\pm 1$  S.E.M. The symbol denotes a significant difference between paired mice and their respective unpaired control mice,  $p < 0.07$ . The asterisk denotes a significant difference between Paired-2.0 Prazosin mice and their respective vehicle control mice at different time points,  $p < 0.05$ .

**Figure 4.**

Results of Chamber Days 1 and 4 of the Conditioning Phase (Panel A) and Test Day 1 (Conditioning Test; Panel B) for paired and unpaired mice of Experiment 2. Time course results of Test Day 1 for paired and unpaired mice of Experiment 2 (Panel C). The error bars represent  $\pm 1$  S.E.M. The asterisks denote a significant difference between Paired-Prazosin and Paired-Vehicle mice,  $ps < 0.06$ .



**Figure 5.** Results of Test Day 2 (Methamphetamine Challenge) for paired and unpaired mice of Experiment 2 (Panel A). Time course results of Test Day 2 for paired and unpaired mice of Experiment 2 (Panel B). The error bars represent  $\pm 1$  S.E.M. The asterisks denote a significant difference between Paired-Prazosin and Paired-Vehicle mice,  $p_s < 0.06$ .



**Figure 6.** Results of Chamber Days 1 and 4 of the Conditioning Phase (Panel A), Test Day 1 (Conditioning Test; Panel B) and Test Day 2 (Methamphetamine Challenge; Panel C) for paired and unpaired mice of Experiment 3. The asterisks denote a significant difference between Paired-Prazosin and Paired-Vehicle mice,  $p < 0.05$