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Research report

Time-dependent effects of prazosin on the development of methamphetamine conditioned hyperactivity and context-specific sensitization in mice

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HIGHLIGHTS

- Examined role of α_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.

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ABSTRACT

The present experiments examined the effects of prazosin, a selective α_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 min *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 h (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-h 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 α_1-adrenergic receptor mediates the development of methamphetamine-conditioned hyperactivity and context-specific sensitization, perhaps by altering memory consolidation and/or reconsolidation processes.

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

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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_1 or D_2) 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_1-dopamine receptor is further supported by studies employing genetic manipulations (e.g., gene knockout). For example, D_1-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_3-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 α_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_1 and A_2 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 α_1-adrenergic receptor, neurons that release dopamine, leading to increased D_1- and D_2-dopaminergic receptor activity downstream [16]. Electrophysiological studies have shown that stimulation of α_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 α_1-adrenergic receptors with the selective α_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 α_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 α_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, α_{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 α_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 α_1-adrenergic receptor. Thus, in Experiment 1, prazosin was administered at various doses (0.5, 1.0 or 2.0 mg/kg) 30 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 (<24 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.

2. Materials and methods

2.1. Subjects

Male, adolescent Swiss-Webster mice ($n = 160$) were obtained from Charles River Laboratories (Raleigh, NC). 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 (Carefree Ultra). Food (Purina Fortified Rodent Chow) and water were made available ad libitum. The room was kept at ~21 °C 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