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The differential effects of alprazolam and oxazepam on methamphetamine self-administration in rats

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ABSTRACT

Background: Methamphetamine is the second most commonly used illicit drug in the world, and despite recent attempts by the Drug Enforcement Administration to combat this epidemic, methamphetamine use is still on the rise. As methamphetamine use increases so does polydrug use, particularly that involving methamphetamine and benzodiazepines. The present study was designed to examine the effects of two benzodiazepines on methamphetamine self-administration.

Methods: Five doses of methamphetamine (0.0075, 0.015, 0.03, 0.09, and 0.12 mg/kg/infusion) were tested, producing an inverted U-shaped dose-response curve. Rats were then pretreated with oxazepam, alprazolam, or vehicle prior to methamphetamine self-administration. To determine if the effects of these drugs were due to the $GABA_A$ receptor and/or translocator protein (TSPO), we also pretreated rats with an antagonist for the benzodiazepine-binding site on the $GABA_A$ receptor (i.e., flumazenil) and a TSPO antagonist (i.e., PK11195) prior to alprazolam or oxazepam administration.

Results: Oxazepam significantly reduced methamphetamine self-administration as demonstrated by a downward shift of the dose-response curve. In contrast, alprazolam significantly enhanced methamphetamine self-administration as evidenced by a leftward shift of the dose-response curve. Flumazenil completely blocked the effects of alprazolam on methamphetamine self-administration. When administered individually, both flumazenil and PK11195 partially reversed the effects of oxazepam on methamphetamine self-administration. However, when these two antagonists were combined, the effects of oxazepam were completely reversed.

Conclusions: The $GABA_A$ receptor is responsible for the alprazolam-induced enhancement of methamphetamine self-administration, while the activation of both the $GABA_A$ receptor and TSPO are responsible for the oxazepam-induced reduction of methamphetamine self-administration.

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1. Introduction

Methamphetamine is a highly addictive psychostimulant that is one of the most widely abused drugs in the United States as well as worldwide (Courtney and Ray, 2014; Romanelli and Smith, 2006). Recent studies have demonstrated that methamphetamine use is linked with a diminished quality of life, including violence, impaired everyday functional ability, and risk-taking behaviors (Henry et al., 2010; Costenbader et al., 2007; Sommers et al., 2006; Anderson and Bokor, 1998). Despite the serious negative consequences associated with methamphetamine use, there are still no FDA-approved pharmacological treatments for methamphetamine dependence (Elkashef et al., 2008). Although psychotherapy is the mainstay of treatment for methamphetamine addiction, it is not very effective as evidenced by high relapse rates (Brecht and Herbeck, 2014; McKetin et al., 2012; Rawson et al., 2002). Thus, more effective treatments for methamphetamine dependence are needed.

Over the last twenty-five years, our lab has shown a strong relationship between stimulant reinforcement and stress, particularly the activation of the hypothalamic-pituitary-adrenal (HPA) axis (Goeders, 2002, 2004, 2007; Goeders and Guerin, 1994). In that regard, we have investigated the effects of drugs that attenuate HPA axis activity on cocaine self-administration. Benzodiazepine-like drugs represent one class of drugs effective in reducing cocaine-taking behavior in rats (Goeders et al., 1993; Goeders and Guerin, 2008). Among the various benzodiazepine receptor agonists tested

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were alprazolam and oxazepam, and we reported that both of these drugs reduced cocaine taking in rats (Goeders et al., 1993; Goeders and Guerin, 2008).

We found similar results using oxazepam in a cocaine and methamphetamine discrimination task, whereby oxazepam reduced the apparent discriminative stimulus effects of both cocaine and methamphetamine in rats (Spence et al., 2015). However, we discovered that alprazolam affected cocaine and methamphetamine drug discrimination differently. Surprisingly, while alprazolam did not alter cocaine discrimination, it actually augmented the discriminative stimulus effects of methamphetamine so that less methamphetamine was required to produce similar methamphetamine-appropriate responding as in the absence of alprazolam (Spence et al., 2015). The results of these experiments suggested that these two benzodiazepine receptor agonists could produce seemingly opposite effects on the discriminative stimulus effects of methamphetamine.

Since it was not clear whether or not these differential effects were specific for drug discrimination or would carry over to other cocaine- and methamphetamine-related behaviors, we conducted the current study to determine the effects of these benzodiazepines on methamphetamine self-administration. We hypothesized that oxazepam would reduce while alprazolam would enhance methamphetamine self-administration.

Although oxazepam and alprazolam have similar affinities for the $GABA_A$ receptor, these benzodiazepines have different affinities for the translocator protein (TSPO; Schmoutz et al., 2014). Previous findings in our laboratory have shown that oxazepam binds to and activates the TSPO, while alprazolam does not (Schmoutz, 2013). TSPO activation stimulates the formation of neurosteroids, which have been suggested to play a role in addiction (Costa et al., 1994; Papadopoulos et al., 1992; Doron et al., 2006). Previous experiments have shown that neurosteroids reduce the self-administration of ethanol and cocaine (Besheer et al., 2010; Anker et al., 2010; Doron et al., 2006; Schmoutz, 2013) and can block the rewarding properties of drugs of abuse (Romieu et al., 2003; Russo et al., 2003).

To determine if these benzodiazepines' affinities for the TSPO and/or $GABA_A$ receptors could be responsible for their effects on methamphetamine self-administration, we pretreated rats with a TSPO antagonist (i.e., PK11195) and an antagonist for the benzodiazepine-binding site on the $GABA_A$ receptor (i.e., flumazenil) prior to alprazolam or oxazepam administration. We hypothesized that flumazenil would block the effects of both oxazepam and alprazolam while PK11195 would only inhibit the effects of oxazepam on methamphetamine self-administration.

2. Materials and methods

2.1. Subjects

Adult male Wistar rats (Harlan Sprague Dawley, Indianapolis, IN), 80–100 days old at the start of the experiment were used. Female rats were not included in the present study since our previous data suggested that alprazolam and oxazepam produce similar effects on methamphetamine-related behaviors in both male and female rats (Spence et al., 2015). Rats were maintained at 85–90% of their free-feeding body weights by daily feedings of approximately 14 g of food (Purina Rat Chow) immediately following their self-administration session with free access to water. The average weight for rats at the beginning of the study was 337.4 g, and their average weight upon completion of the study was 336.8 g. Rats were individually housed in cages equipped with a laminar flow unit and air filter in a temperature- and humidity-controlled, AALAC-accredited animal care facility on a reversed 12-h light, 12-h dark cycle (lights on at 18:00). Rats (n = 16) were randomly divided into two groups (n = 8/group). Six rats did not complete all of the experiments due to complications associated with the experimental procedure, such as catheter failures or the failure to achieve stable baselines of methamphetamine self-administration. The first group of rats was treated with vehicle and alprazolam, and the second group was treated with vehicle and oxazepam. Both experimental groups received similar extinction training. All procedures were carried out in accordance with the "Public Health Services Policy on Humane Care and Use of Laboratory Animals" and the "Guide for the Care and Use of Laboratory Animals" Eighth Edition, 2011 and were approved by the Louisiana State University Health Sciences Center in Shreveport Institutional Animal Care and Use Committee.

2.2. Apparatus

Behavioral experiments were conducted in standard Plexiglas and stainless steel, sound-attenuating operant conditioning chambers (Med-Associates, St. Albans, VT). The operant chambers were equipped with a retractable response lever mounted on one wall of the chamber, with a stimulus light located above the lever. The chamber was also equipped with an exhaust fan that supplied ventilation and masked extraneous sounds. Programming and data collection were performed using Med-PC software and interface system and an IBM-compatible computer.

2.3. Surgical procedure

Before undergoing any surgical procedures, the rats were allowed at least one week to acclimate to the facility. Then, once the targeted weight was reached (i.e., 85–90% of their free-feeding body weights), the rats were implanted with chronic indwelling jugular catheters (Keller et al., 2013). Prior to this surgery, rats were anesthetized with pentobarbital (50 mg/kg, i.p.) and pretreated with atropine methyl nitrate (10 mg/kg, i.p.) to reduce bronchial secretions and penicillin G procaine suspension (75,000 units, i.m.) to prevent infections. Silicon tubing, Marlex mesh, and a 22-gauge guide cannula were used to construct and secure the catheters. An opening was made in the rat's neck so that the catheter was inserted into the jugular vein. Once inserted into the vein, the catheter was secured to the vein and continued under the scapula to the back, where the skin was sutured around the guide cannula.

2.4. Methamphetamine self-administration

Following all surgical procedures, the rats were allowed a minimum of five days to recover before initiating self-administration training. Rats were trained to self-administer methamphetamine (0.06 mg/kg/infusion) during daily 2-h sessions, Monday-Saturday. Subjects were initially trained under a fixed-ratio of 1 (FR1) schedule of reinforcement, which was gradually increased to FR2 and finally to FR4, so that four depressions of the lever resulted in an infusion (200 μl in 5.6 s) of methamphetamine, which traveled through Tygon tubing contained within a spring leash. This leash was attached to a liquid swivel contained within a counterbalanced arm to allow relatively unrestricted movement of the animals.

The availability of methamphetamine was indicated by the illumination of a stimulus light located directly above the response lever. During the infusion, the stimulus light was extinguished and remained extinguished for a 20-s time-out period following the infusion. During this period, responses were recorded but did not result in an infusion of methamphetamine.

Prior to testing with alprazolam or oxazepam, the rats were exposed to extinction training. During extinction, the methamphetamine syringe was replaced with a saline syringe and responses on the lever only resulted in an infusion of saline.