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The effects of alprazolam on conditioned place preferences produced by intravenous heroin

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Abstract

Case studies reveal that opiate addicts often self-medicate with benzodiazepine (BDZ) tranquilizers prior to taking their opiate. Our laboratory has previously utilized the conditioned place preference paradigm to confirm that BDZs can augment the affective response to heroin in laboratory animals. The combination of alprazolam and varying doses of intravenous heroin resulted in a leftward shift of the heroin dose–response curve. The present experiment was devised to extend the previous findings by examining the ability of varying alprazolam doses (0.125, 0.25, or 0.5 mg/kg ip) to potentiate the reward of a single challenge dose of heroin (0.025 mg/kg iv). The results demonstrate that a nonrewarding dose of alprazolam (0.125 mg/kg) and intravenous heroin can interact to produce reliable place preferences. The data thereby support prior work from our laboratory regarding the synergistic actions of BDZs and opiates.

Keywords: Heroin; Opiate; Alprazolam; Benzodiazepine; Place preference; Reward; Reinforcement; Drug interaction

1. Introduction

Clinical research has suggested that human opiate users often self-administer benzodiazepines (BDZs) either prior to or concurrently with opiates (Stitzer et al., 1981; Preston et al., 1984; Weddington and Carney, 1987; Navatanam and Foong, 1990; Forsyth et al., 1993; Iguchi et al., 1993). The primary explanation for this coabuse is the reported potentiation of the opiate reward experience produced by the BDZ pretreatment (Stitzer et al., 1981; Navatanam and Foong, 1990; Iguchi et al., 1993; Gelkopf et al., 1999). Of course, this also suggests a possible secondary financial incentive in that BDZ pretreatment may permit the user to experience a comparable euphoric effect with a smaller dose of opiate, and hence, extend the number of dosing that a given quantity of opiate can provide (Navatanam and Foong, 1990).

The prevalence of opiate + BDZ coabuse is widespread with reports from Europe, Asia, the Middle East, Australia, and the United States (Segura et al., 2001; Gelkopf et al., 1999; Darke et al., 1995; Iguchi et al., 1993; Navatanam and Foong, 1990) verifying it's existence. For example, 99% of the patients that had entered an opiate detoxification center in Malaysia reported that they had coabused opiates and BDZs within the 24-h period prior to detoxification (Navatanam and Foong, 1990). Another recent clinical report focusing on BDZ use in methadone treatment centers located in Spain established that opiate + BDZ coabuse was occurring in 48% of their patient population (Segura et al., 2001). A similar analysis provided by an Israeli study found that 66.6% of the patient population abused BDZs in the 12-month period before beginning methadone maintenance, with 41.4% of those patients reporting the use of BDZs to enhance the effect of another drug (Gelkopf et al., 1999).

In order to systematically study the neural mechanisms by which BDZs might potentiate opiate reward, Walker and Ettenberg (2001) utilized the conditioned place preference test in laboratory animals to measure the rewarding effects of BDZ–opiate interactions. The results of the study indicated a single dose of the BDZ, alprazolam, potentiated the rewarding properties of a low heroin dose (0.025 mg/kg iv) that was itself nonrewarding, but attenuated the response produced by a previously rewarding dose of heroin (0.1 mg/kg). Essentially, the alprazolam challenge appeared to shift the heroin-induced dose–response curve for conditioned place preferences to the left—a result consistent with the clinical reports of BDZ potentiation of opiate actions.

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The present study was devised to replicate and extend these results by assessing the ability of varying doses of alprazolam to alter the response to a subrewarding dose of intravenous heroin. It was of particular interest to assess whether low doses of alprazolam might act synergistically with a subrewarding dose of heroin to produce a positive affective response as measured in the conditioned place preference test.

2. Methods

2.1. Animals

The subjects were 63 male Sprague–Dawley rats (each weighing 250–350 g) obtained from Charles River Laboratories (Wilmington, MA). Each rat was individually housed in hanging wire-mesh cages located within a temperature-controlled (23 °C) vivarium that was maintained on a 12-h light/dark cycle (lights on at 0700). Food and water were freely available throughout the entire course of the experiments. Upon their arrival in the vivarium, animals were gentled through daily handling over a 1-week period (i.e., until surgery). The work described in our paper adheres to the guidelines stipulated in the NIH Health Guide for the Care and Use of Laboratory Animals and was reviewed and approved by UCSB's Institutional Animal Care and Use Committee.

2.2. Surgery

Each animal was implanted with an intravenous catheter inserted into the jugular vein. Surgery was conducted under deep anesthesia produced by 50 mg/kg ip sodium pentobarbital supplemented by 100 mg/kg ip chloral hydrate. Catheters consisted of polyethylene tubing (PE20) that was beveled on the end inserted into the jugular vein. An incision above the left jugular vein was made by the use of a scalpel and the underlying tissue was dissected to expose the jugular vein. After puncturing the vein, the beveled end of the catheter was carefully inserted into the resulting breach. Once inserted, the catheter was secured in place to the underlying tissue by suture. The open end of the catheter was glued to a threaded cannula guide (Plastic Product, Roanoke, VA) that was passed subcutaneously behind the shoulder to a central position on the back where the guide exited the dermal and cutaneous layers via a small biopsy hole (3 mm diameter). The cannula guide was affixed to a 3-cm square of high-density polyethylene mesh (Marlex) that was sutured in place subcutaneously on the animal's back. A dummy cannula was screwed down into the open guide in order to seal the system. Postsurgical handling consisted of daily weighing and intravenous administration of the antibiotics ticarcillin disodium and clavulanate potassium (Timentin; 20 mg) in 0.1 ml 0.9% physiological saline for a 1-week period. The intravenous catheters were flushed daily following conditioning trials with 0.1 ml heparinized (100 IU/ml) physiological saline to maintain catheter patency.

2.3. Apparatus

The place preference apparatus consisted of a wooden rectangular enclosure measuring $156.25 \times 34.3 \times 30.5$ cm (length × width × height) that was divided into three chambers; two larger compartments (61×30.5 cm) at either end (one black and one white) and a middle gray zone (26.5×30.5 cm) separating the two. The black side of the apparatus had an acrylic (Plexiglas) floor while the floor of the white compartment was covered with wood chip bedding that was changed prior to each trial. The middle zone had a wooden floor painted gray. Prior to each trial, the black walls were wiped (5 cm from the floor) with a cotton pad moistened with 0.1 ml of 2% acetic acid solution. This introduced a distinct olfactory cue to the black compartment that was not present in the neutral or white compartments. The apparatus, therefore, provided three distinct environments that differed in color, texture, and odor. Additionally, the walls within the apparatus that separated the environments were removable so that an animal could be permitted to walk freely between the three environments during place preference testing.

Fifteen infrared emitter/detector pairs were installed at approximately 10-cm intervals 2 cm above the floor along the entire length of the place preference apparatus. The output of the detectors permitted automated data collection of the animal's location within the apparatus in real time. An animal was operationally defined as being "within" a compartment when the number of infrared photocells interrupted in the compartment being entered was higher than the number of interrupted beams for the compartment being exited (i.e., typically requiring two-thirds of the subject's body to be within a compartment). A PC with a custom I/O board and running custom software collected these data.

2.4. Drugs

The BDZ, alprazolam, was purchased from Sigma Pharmaceuticals (St. Louis, MO) and prepared in a vehicle solution consisting of 8% ethanol, 42% propylene glycol, and 50% physiological saline (it is not soluble in water or saline). Alprazolam was administered in a volume of 1 ml/kg with doses ranging from 0.125 to 0.5 mg/kg ip. Diacetylmorphine (heroin) was obtained from the National Institute on Drug Abuse (NIDA; Rockville, MD) and was prepared in a vehicle solution of 0.9% physiological saline. The dose of heroin utilized was 0.025 mg/kg iv delivered in a volume of 0.1 ml over a 5.6-s injection interval.

Following the completion of the study, all animals were infused with 0.1 ml iv 1% methohexitol (Brevital), a fast-acting barbiturate, to produce a loss of consciousness and thereby confirm the patency of the catheters.

2.5. General procedure

The experiment consisted of a 10-day protocol that involved pre- and postconditioning place preference tests separated by 8 days of drug–place conditioning.

2.5.1. Baseline

On Day 1 of the procedure, an initial baseline was conducted in the place preference apparatus with the walls removed to provide the subjects with complete access to the three test environments. Each animal was placed in the middle (gray) compartment of the apparatus and the time spent in each of the three environments was then recorded over a 15-min session. Upon completion of the trial, the animals were removed from the apparatus and returned to their home cages. The apparatus was then completely cleaned prior to the next animal's trial.

2.5.2. Conditioning trials

Days 2–9 were conditioning trials during which the walls of the apparatus were set in place and the animals were restricted to either the black or white compartments. On a given day, each animal received either vehicle or drug followed by placement into either the black or white side of the apparatus for 15 min. On the next day, the animal received the alternate treatment and was placed in the alternate environment. This continued for 8 days after which each animal had experienced four drug pairings with one side of the apparatus and four saline pairings with the opposite side. The procedure was counterbalanced within each group for injection order (saline or drug) and the color of the compartment that was paired with the drug.

2.5.3. Test trial

Day 10 was an undrugged preference test conducted with the walls removed precisely as described for the initial baseline preference test.

2.6. Alprazolam dose–response curve

Twenty-seven intravenously catheterized animals were randomly assigned to one of three groups ($n = 9$) corresponding to different doses of alprazolam (0.125, 0.25, and 0.5 mg/kg ip). These animals were administered with alprazolam 20 min prior to an intravenous saline infusion that occurred immediately before placement into either the black or white side of the apparatus on the four drug conditioning trials. On alternate days, the alprazolam vehicle and an intravenous saline infusion were paired with the alternate environment. Intravenous infusions were accomplished via the insertion of an internal cannula that was threaded into the guide cannula secured to the animal's back. Intravenous infusions (0.1 ml) were controlled by the use of a 5-rpm Razel syringe pump loaded with a 10-ml syringe (Stanford, CT, Model A). Ten seconds after the infusions were completed, animals were disconnected from the system and immediately placed into their assigned conditioning compartment for 15 min. Following the completion of a conditioning trial, each animal was removed from the apparatus and individually transported to the vivarium where its catheter was flushed with 0.1 ml heparinized (100 IU/ml) physiological saline, prior to placement in its home cage.

2.7. Heroin+alprazolam dose–response challenge

Thirty-six intravenously catheterized animals were randomly assigned to one of four groups ($n = 9$), each corresponding a different dose of alprazolam (0.0, 0.125, 0.25, and 0.5 mg/kg ip). In all animals, the alprazolam treatment was followed by a heroin (0.025 mg/kg iv) infusion. The dose of heroin (0.025 mg/kg) was selected to be subthreshold in producing conditioned place preferences (Walker and Ettenberg, 2001). For each group, a 10-day place preference procedure was conducted as already described. Alprazolam was injected intraperitoneally 20 min prior to an intravenous heroin infusion. On alternate days, the intraperitoneal vehicle for alprazolam was injected 20 min prior to intravenous saline. Subjects were immediately placed into their assigned compartment each day after the intravenous infusion. The final test trial, then, afforded the nondrugged subjects a choice between an environment previously associated with alprazolam + heroin and an alternate environment paired with the two vehicle solutions.

2.8. Data analysis

Conditioned place preferences are operationally defined as reliable shifts from baseline to test in the time spent in a drug-paired environment following drug–place conditioning. Thus, for example, an opiate-induced place preference would be identified as an increase in the time spent on the opiate-paired side of the apparatus on test day relative to baseline. To facilitate this analysis, 'difference scores' were computed for each animal by subtracting the time spent in the drug-paired environment during the baseline trial (prior to conditioning) from the time spent there postconditioning (test day). Mean difference scores for each group were then compared using independent-sample one-way analyses of variance (ANOVAs). Note that in this situation, a conditioned place preference necessarily requires that the difference between test day and baseline performance be reliably different from zero. Hence, planned post hoc analyses consisted of simple one-sample t tests (two-tailed) where each group's difference score was compared to zero.

3. Results

An assessment of the mean time spent in the black versus white compartments during baseline across all animals ($N = 63$) confirmed the lack of any position bias [mean ±

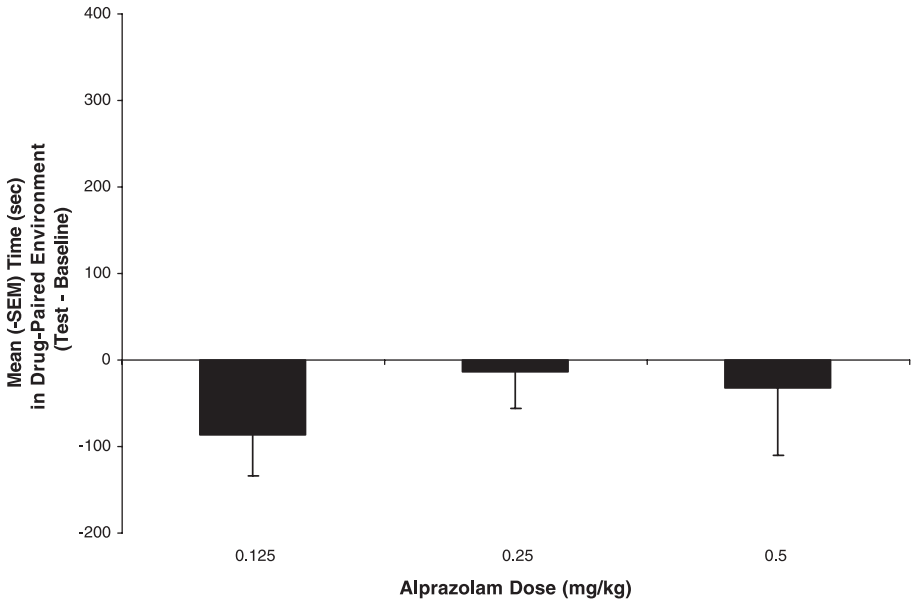

Fig. 1. Mean (−S.E.M.) difference scores (Test−Baseline) for animals having experienced intraperitoneal alprazolam−place pairings. Scores below the line indicate shifts away from the drug-paired side on test day relative to baseline. Alprazolam pretreatments did not in and of themselves produce reliable shifts in conditioned place preferences.

S.E.M. time on white side = 319 ± 18, black side = 300 ± 20; paired sample t test, $t(62) = 0.61$, n.s.]. Fig. 1 depicts the shift in preference for an environment paired with one of the three doses of alprazolam—0.125, 0.25, and 0.5 mg/kg. The ANOVA confirmed that the change in performance from baseline to test did not differ across alprazolam doses [i.e., across groups; $F(2,25) = 0.720$, $P > .05$]. Additionally, post hoc one-sample t tests confirmed that none of the alprazolam doses differs significantly from zero ($P > .05$). Thus, when administered 20 min prior to conditioning, none of the doses tested produced reliable preferences for the alprazolam-paired environment.

Fig. 2 depicts the shift toward the drug-paired side of the apparatus in subjects treated with alprazolam + heroin. The ANOVA conducted on the difference scores presented in Fig. 2 identified a marginal main effect for group

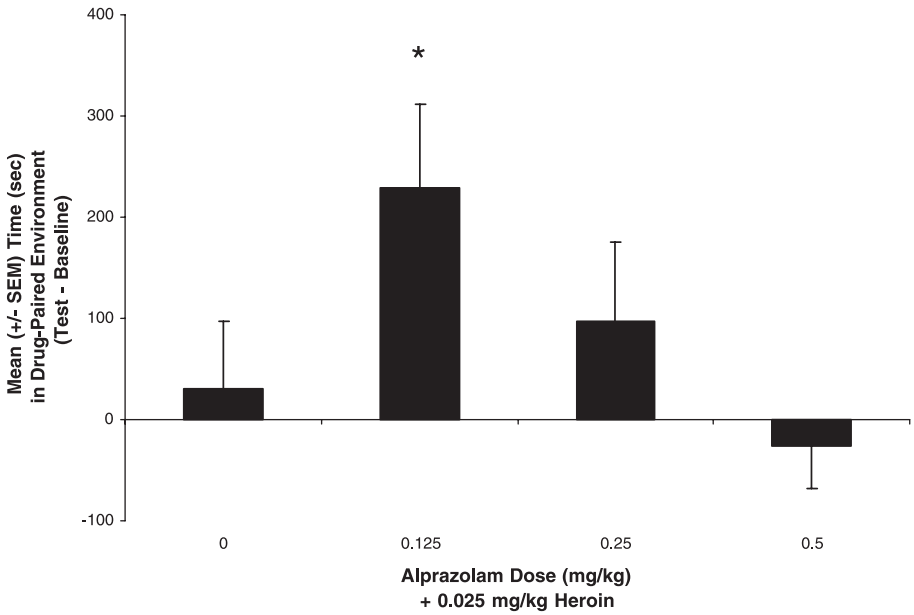

Fig. 2. Mean (±S.E.M.) difference scores (Test−Baseline) for animals having experienced pairings of a distinctive environment with varying doses of ip + 0.025 mg/kg iv heroin. Scores above or below the line represent shifts toward or away from the drug-paired side of the apparatus on test day relative to baseline (* = $P < .005$ when compared to zero).

[$F(3,35) = 2.778$, $P = .057$]. Post hoc least significant difference (LSD) tests identified that the combination of 0.125 mg/kg ip alprazolam and 0.025 mg/kg iv heroin was reliably different than heroin (0.025 mg/kg) alone or in combination with 0.5 mg/kg ip alprazolam ($P < .05$). Preplanned, one sample t tests indicated that only the 0.125 mg/kg ip alprazolam + 0.025 mg/kg iv heroin group displayed a place preference that was reliably different from zero [$t(8) = 2.78$, $P < .05$]. Thus, a dose of heroin (0.025 mg/kg iv) that itself produced no reliable conditioned place preference, when combined with a dose of alprazolam (0.125 mg/kg ip) that similarly had no effect in the place preference test (Fig. 1), produced a reliable shift in preference toward the heroin + alprazolam-paired environment (Fig. 2).

4. Discussion

The results of the present experiment replicate earlier findings (Walker and Ettenberg, 2001) that the preference for a distinctive place associated with intravenous heroin can be potentiated by pretreatment with the BDZ alprazolam. In the present study, alprazolam treatment alone failed to shift the animal's behavior from baseline at all doses tested (see Fig. 1). However, when challenged with a dose of heroin (0.025 mg/kg iv) that was itself nonrewarding (Walker and Ettenberg, 2001), a small dose of alprazolam (0.125 mg/kg) produced a robust conditioned place preference for the drug-paired environment (see Fig. 2). The data thereby confirm results from the clinical literature (Stitzer et al., 1981; Navatanam and Foong, 1990; Iguchi et al., 1993; Gelkopf et al., 1999) that the combination of BDZs and opiates can have additive or even synergistic effects.

Walker and Ettenberg (2001) established that BDZ pretreatments shifted the dose–response curve for intravenous heroin to the left in the conditioned place preference test. The current results complimented and extended those findings by showing that increasing BDZ receptor activation similarly potentiated the effects of intravenous heroin. Hence, it would appear that the underlying substrates of the place preferences produced by alprazolam + heroin are equally susceptible to either opiate or BDZ receptor modulation.

Opiate + BDZ interactions have been identified in nociceptive and respiratory systems that are consistent with the present results. Alprazolam has been shown to facilitate morphine-induced analgesia in the tail-flick assay (Bianchi et al., 1993). Additionally, an interaction has been shown to exist for inducing respiratory depression between alprazolam and dermorphin, a selective μ-opiate receptor agonist (Paakkari et al., 1993).

While the present data suggest that the BDZ pretreatment is enhancing the unconditioned effects of the heroin stimulus in the place preference paradigm, it remains unknown whether it is doing this through positive or negative reinforcement mechanisms or whether the enhanced drug reward observed in this work results from BDZ and opiate actions at the same neural sites or through independent, but additive mechanisms. One approach to the second question would be to identify brain sites known to have significant concentrations of both BDZ and opiate receptors. Because BDZ receptor sites modulate $GABA_a$ receptors (Hunkeler et al., 1981; Richards et al., 1986; Martin, 1987), populations of cell bodies expressing $GABA_a$ receptors that have previously shown to be involved with reinforcement systems would be of interest. For example, the ventral tegmental area of the mammalian mesencephalon (midbrain) has been proposed as a critical site for opiate reinforcement (Phillips and LePaine, 1980; Bozarth, 1987; Bozarth and Wise, 1981). μ-Opiate receptors are localized on inhibitory interneurons that, when stimulated, cause a disinhibition of dopamine (DA) neurons and a consequent increase in DA release in the nucleus accumbens (Johnson and North, 1992)—a site that is believed to play a critical role in drug reward (Koob et al., 1997; De Vries and Shippenberg, 2002; Everitt and Wolf, 2002; Maldanado and de Fonseca, 2002; Picciotto and Corrigall, 2002). $GABA_a$ receptors (and thus BDZ receptors) are thought to be colocalized with opiate receptors on inhibitory interneurons within the VTA (Xi and Stein, 1998), and $GABA_a$ receptor agonists administered into the ventral tegmental area (VTA) produce a disinhibitory effect on DA release in the nucleus accumbens (Xi and Stein, 1998). Within the nucleus accumbens itself, opiate and $GABA_a$ receptor sites have also been shown to be colocalized on the dendrites of GABAergic neurons (Svingos et al., 1997). These data suggest that the synergistic effects of alprazolam and heroin may be mediated through similar actions at a common neural site—the mesolimbic dopamine system.

Another possibility is that the critical site(s) where alprazolam is acting to influence heroin reward is spatially separate from opiate reward elements, but that the two regions either interact (via a common final pathway) or produce effects that sum to reach suprathreshold reward levels. For example, it is entirely possible that the BDZs are operating as negative reinforcers by attenuating preexisting levels of anxiety (and working through nonDA systems) while heroin is acting more directly to produce positive affect or euphoria through DA or endogenous opiate systems. Indeed, the amygdala has been implicated as a potential substrate for the anxiolytic actions of BDZs (Menard and Treit, 1999), and particularly the basolateral amygdala, which is known to have a high density of BDZ receptors (Niehoff and Kuhar, 1983). The basolateral amygdala is of additional interest because of its anatomical connectivity with the nucleus accumbens (Setlow et al., 2002).

In sum, the current work establishes an important interactive relationship between opiate and BDZ drug classes and provides some basis for the behavior of opiate abusers

who premedicate with BDZs. Additional work is underway to more clearly establish whether the two drugs in question are acting at common or separate neural sites.

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