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Anxiolytic-like actions of buspirone in a runway model of intravenous cocaine self-administration

Aaron Ettenberg *, Rick E. Bernardi

Behavioral Pharmacology Laboratory, Department of Psychology, University of California, Santa Barbara, CA 93106-9660, United States

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Abstract

In previous work from our laboratory, rats traversing a straight alley for a reward of IV cocaine have been observed to develop ambivalence about entering the goal box. Over trials, animals repeatedly run toward the goal box, stop at the entry point, and then retreat back toward the start box. This unique pattern of retreat behavior has been shown to reflect a form of "approach–avoidance conflict" that stems from the subjects' concurrent positive (cocaine reward) and negative (cocaine-induced anxiety) associations with the goal box. Buspirone, a partial 5-HT_{1A} agonist, has been reported to produce anxiolytic-like actions in the clinic, but has had mixed results in experimental tests of anxiety using animal subjects. Since most animal tests of conflict/anxiety employ the administration of foot-shock – a relatively strong aversive stimulus – it was of interest to determine whether buspirone would alter the more subtle approach–avoidance conflict observed in well-trained animals running a straight alley for single daily injections of 1.0 mg/kg IV cocaine. Runway testing consisted of single daily trials that continued until consistent approach–avoidance retreats were exhibited. Each animal was then pretreated 30 min prior to runway testing with vehicle and one of three doses of buspirone (0.0, 1.0, 2.5 or 5.0 mg/kg IP). Testing continued in a counterbalanced manner until all rats had experienced each dose of buspirone with 3 days of cocaine-only trials between each test day. The number of retreats exhibited on each trial served as an index of the approach–avoidance conflict present on that trial. Results clearly demonstrated that buspirone (at the two higher doses) attenuated the retreat behavior of animals approaching a goal box for IV cocaine — an action consistent with its anxiolytic-like actions in the clinic.

Keywords: Anxiety; Approach–avoidance conflict; Retreats; Drug reward; Serotonin

1. Introduction

The positive attributes of IV cocaine are well documented — the drug is readily self-administered by humans (Fischman and Schuster, 1982; Lynch et al., 2006) and animals (e.g., see reviews by Fibiger et al., 1992; Folton and Fischman, 1994; Porrino et al., 2004; Wolverton, 1992), it produces learned preferences for distinct locations paired with its delivery (Bardo et al., 1995; Calcagnetti et al., 1995; Carr et al., 1989), it lowers the threshold for rewarding brain stimulation (Gill et al., 2004; Gilliss et al., 2002) and is subjectively described by human users as positive/euphoric in nature (Lynch et al., 2006; Singha et al., 1999; Walsh and Cunningham, 1997). However, cocaine also has been shown to have aversive or negative attributes whose onsets occur as the initial positive actions of the drug subside. So, for example, while animals learn to prefer locations paired with the immediate effects of IV cocaine (conditioned place preferences), they come to avoid places associated with effects present 15 min post-IV injection (Ettenberg et al., 1999; Knackstedt et al., 2002). Human cocaine users also report that the initial "high" from the drug is often replaced by a strong aversive state characterized by anxiety, agitation and craving (Anthony et al., 1989; Washton and Gold, 1984; Williamson et al., 1997). Cocaine has also been reported to increase thigmotaxic behavior (avoiding the open spaces in an open field; Simon et al., 1994), to exacerbate the behavioral suppressant effects of aversive stimuli or punishment (Dworkin et al., 1989; Fontana and Commissaris, 1989), to heighten the anxiogenic response of animals in an elevated plus maze (Hayase et al., 2005; Paine et al., 2002; Rogerio and Takahashi, 1992), and to potentiate animals' avoidance of an inherently

* Corresponding author. Department of Psychology, University of California, Santa Barbara, CA 93106-9660, United States. Tel.: +1 805 893 3682; fax: +1 805 893 4303.
E-mail address: ettenberg@psych.ucsb.edu (A. Ettenberg).

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aversive environment (Costall et al., 1989). It has also been reported that the intereoceptive cues produced by subjects' exposure to restraint stress, generalize to the discriminative stimulus properties of cocaine (Mantsch and Goeders, 1998).

In the early 1990s, our laboratory demonstrated that IV self-administered cocaine produced evidence of concurrent positive and negative actions in the same animals using a single test procedure. Rats trained to traverse a straight alley for once-a-day injections of IV cocaine (delivered upon goal box entry) develop over trials a unique "retreat behavior" characterized by approach toward and then withdrawal from the cocaine-associated goal box (Ettenberg and Geist, 1991). We have subsequently demonstrated that this retreat behavior closely resembles that which develops in animals approaching a goal box associated with other mixed positive+negative stimuli (e.g., food+foot-shock), that the location of the retreats in the alley (at the threshold of the goal box entry and not randomly distributed in the runway) is consistent with classic theories of approach–avoidance conflict (e.g., Miller, 1944), and that retreat behaviors (like other forms of experimentally-induced conflict/anxiety) is reversed by drugs having known anxiolytic-like actions (Ettenberg and Geist, 1991, 1993; Geist and Ettenberg, 1997; Guzman and Ettenberg, 2004; Knackstedt and Ettenberg, 2005; Raven et al., 2000; see review by Ettenberg, 2004). Retreat behavior would seem to represent an index of the concurrent positive (rewarding) and negative (anxiogenic) actions of self-administered cocaine. Additionally, since the animals exhibit retreat behaviors *prior* to goal box entry (and hence prior to cocaine administration) the data are not subject to the inherent interpretative confounds resulting from cocaine's well-documented psychomotor/nonspecific actions.

As indicated above, we have demonstrated that the ambivalence that animals exhibit about entering a goal box associated with prior administration of IV cocaine, can be reversed by treatment with drugs having known anxiolytic-like properties. For example, Ettenberg and Geist (1991) reported that diazepam pretreatments dose-dependently reversed the approach–avoidance retreat behaviors of rats running an alley for IV cocaine. In the current study, we investigated whether a similar result would be observed in animals pretreated with the 5-HT_{1A} partial agonist, buspirone (Newman-Tancredi et al., 1998; Pecknold, 1994). Buspirone has been widely and successfully used for the treatment of a variety of anxiety-related states in human patients (e.g., Bond et al., 2003; Fulton and Brogden, 1997; Goa and Ward, 1986), however its effects in animal studies, particularly those employing shock-induced conflict/anxiety, have been less effective and/or less consistent compared to more traditional anxiolytic compounds (e.g., Benvenga and Leander, 1996; Martin et al., 1993; Meneses and Hong, 1993; Sanger, 1990; Witkin and Perez, 1989). Since cocaine has potent inhibitory actions at the serotonin transporter (Filip et al., 2005; Koe, 1976; Ritz et al., 1990), and there is a growing literature implicating the 5-HT cells of the dorsal raphé in the modulation of anxiety-related states (e.g., Abrams et al., 2004; Chaouloff, 2000; Sena et al., 2003), it was of interest to assess whether buspirone pretreatment would alleviate the approach–avoidance conflict of animals running an alley for daily infusions of IV cocaine. More specifically, the present study was devised to test the hypothesis that pretreatment with the 5-HT_{1A} partial agonist, buspirone, would alter the approach–avoidance conflict (anxiety) of animals running a straight alley for IV cocaine, and thereby reduce the frequency of behavioral retreats observed in the alley.

2. Methods

2.1. Subjects

The subjects (Ss) in this research were male Sprague Dawley rats (300–325 gm at the time of surgery) obtained from Charles River Laboratories (Wilmington, MA). The animals were housed individually in metal wire hanging cages located within a secure and temperature-controlled 23 °C vivarium. The animals were gentled for a period of 7 days prior to catheterization and were provided ad libitum access to food and water throughout the study. The care and use of the animals, and all aspects of the experimental protocol, were reviewed and approved by the campus IACUC (Institutional Animal Care and Use Committee) for compliance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals.*

2.2. Surgery

Each animal was surgically implanted with a chronic silastic jugular catheter under deep isoflurane-induced anesthesia (4% for induction and 1.4–2.5% for maintenance) administered continuously via inhalation. At the time of surgery, two injections were administered: atropine sulfate (0.04 mg/kg IM) was applied to prevent respiratory congestion, and post-surgical pain was treated with the non-opiate analgesic, flunixin meglumine (FluMe-glumine; 2.0 mg/kg SC). Catheter implantation involved making a small incision in the animal's neck to expose the jugular vein. One end of the catheter was then inserted into the vein and sutured in place. The other end was passed subdermally to the animal's back where it was fused to a threaded guide cannula (Item 313G, Plastics One) that protruded through a small 3 mm diameter opening. The guide cannula was commented to a 2-cm square piece of surgical Mersilene mesh (Ethicon) that was laid flat subdermally on the animal's back and sutured in place. Between test sessions, the open end of the guide cannula was sealed by insertion of a dummy cannula (Item 313DC, Plastics One) that screwed down securely onto the guide. Administration of intravenous heparin or drug was accomplished with an internal cannula (Item 313I, Plastics One) connected by PE 20 tubing to a fluid-filled syringe that was inserted into the open end of the guide cannula (in place of the dummy cannula) and screwed into place so that the Ss' movements would not compromise the connection.

Immediately following the surgery, each animal was administered 50 mg (in 0.25 ml) of the antibiotic the ticarcillin disodium/clavulanate potassium (Timentin) intravenously through the implanted catheter. To ensure catheter patency and reduce the risk of infection, (beginning the day after surgery) each subject was injected daily (beginning the day after surgery) with Timentin

(20 mg/0.1ml IV) followed by heparin (1000 IU/0.1 ml prepared in 0.9% physiological saline) approximately 30 min after runway testing. Runway trials began 10 days after surgery. At the end of the experiment, a low dose of the fast acting barbiturate Brevital (methohexital sodium, 0.1 mg/kg in 0.1 ml) was injected through the IV catheter to confirm catheter patency.

2.3. Drug administration

Cocaine was prepared in a vehicle solution of 0.9% physiological saline and administered in a dose of 1.0 mg/kg IV. The drug was applied in a volume of 0.1 ml/infusion and delivered over a 4.6 s duration via a 10-ml syringe nested in a motorized syringe pump (Razel). Buspirone was similarly prepared in a saline vehicle solution and administered IP in doses of 0.0, 1.0, 2.5 or 5.0 mg/kg in a volume of 2.0 ml/kg.

2.4. Runway apparatus

All behavioral testing was conducted in a single wooden straight-arm runway measuring 155 cm long × 15 cm wide × 40 cm high. Attached at opposite ends of the alley were a start box and goal box of equal dimensions (24 × 25 × 40 cm). The floor of the apparatus consisted of 3 mm diameter steel rods laid in parallel 1.2 cm apart and oriented perpendicular to the sidewalls of the runway. Thirteen infrared photocell emitter–detector pairs were distributed approximately 15 cm apart from one another along the inside walls of the long axis of the runway 2.5 cm above the floor. These infrared sensors were wired to a custom interface that was in turn connected to a desktop computer. The computer ran custom software that recorded the precise location of the animal in the runway in real time throughout each trial. The computer also controlled the opening of the start box door, the closing of the goal box door, and the delivery of the drug reinforcer (i.e., activation of the syringe pump).

Suspended above the alley were two long bar magnets aligned in parallel along the entire length of the apparatus. The magnets served as rails between which a flow-through swivel was located. The swivel was a cylindrically shaped custom-made commutator the top of which was connected by PE tubing to the 10-ml drug-filled syringe and the bottom of which ran down to the guide cannula on the animal's back. A flat circular disk served as a collar around the swivel and prevented it from falling through the space between the two magnetic rails. The swivel permitted the animal to turn and move throughout the apparatus without disconnecting itself from the drug delivery system and without tangling the PE tubing that ran from the swivel to the animal's back. As the subject ran down the alley, it essentially pulled behind and above it the swivel that moved along between the two magnetic rails. To minimize the weight and hence the pull of the swivel on the animal's back, a pot magnet was affixed to the underside of the swivel's collar. The polarity of the pot magnet and the polarity of the rails were aligned so as to repel one another. As a result, the swivel literally floated above the top of the rails and thereby produced minimal resistance to the animal as it moved about within the runway below. For a more complete description of the runway apparatus, see Geist and Ettenberg (1990).

2.5. Procedure

Behavioral testing involved connecting an animal to the drug delivery system by threading the internal cannula (connected by PE 20 tubing to the swivel, which was in turn connected to the drug-filled syringe) into the guide cannula on the animal's back. The animal was then placed into the start box (with the start door closed) for 5 s. The start box door then opened and the animal was provided access to the entire runway. Upon the subject's goal box entry, an infrared sensor signaled the computer to raise the goal box door and then activate the syringe pump for delivery of a single 1.0 mg/kg IV infusion of cocaine. Each animal was restricted to the goal box for 5 min post-infusion and then removed from the apparatus, disconnected from the drug delivery system, and returned to its home cage.

Subjects ($n=6$) were tested in the runway once each day until retreat behaviors had developed in all animals (19 trials/day). Subjects then experienced a saline/vehicle pretreatment 30 min prior to a single cocaine-reinforced runway trial. The next day, each animal was injected with one of the three doses of buspirone (1.0, 2.5 or 5.0 mg/kg IP) and again tested in the runway. Three additional cocaine-runway trials were conducted, followed on consecutive days by another saline pretreatment trial and then a buspirone pretreatment trial. This protocol continued for a third cycle after which every subject had experienced three saline/vehicle pretreatments and all three buspirone doses. This within-group design was conducted in a counterbalanced manner.

The dependent variable in this study was the number of behavioral retreats exhibited by the animals on each of the saline and buspirone trials. A "retreat" was defined as a stop in forward locomotion followed by a return back toward the start box. As described in the Introduction of this paper, our laboratory has demonstrated that this behavior provides a reliable and valid index of the approach–avoidance conflict exhibited by animals entering a goal box associated with the concurrent positive (rewarding) and negative (anxiogenic) properties of cocaine. Goal times were not recorded in this study since our own previous work has shown them to be confounded by, and highly correlated with, retreat behaviors (e.g., Ettenberg and Geist, 1991). Put simply, in this unique situation (where IV cocaine is the reinforcing stimulus delivered upon goal box entry), long goal times do not reflect Ss' low motivation to seek the goal — indeed the animals continue to run very quickly in these situations. The long goal times of animals running for cocaine reflect the fact that the animals are making numerous approaches and retreats to and from the goal box. Since we have found changes in goal times to be accounted for almost entirely by changes in retreat frequency (retreating subjects naturally take long to get to the goal box), and since retreat frequency provides more face validity for the study of cocaine's mixed positive+negative properties, retreats serve as a more meaningful dependent variable in this work.

3. Results

The mean (+SEM) number of retreats exhibited by animals running for cocaine following IP pretreatment with 0.0, 1.0, 2.5

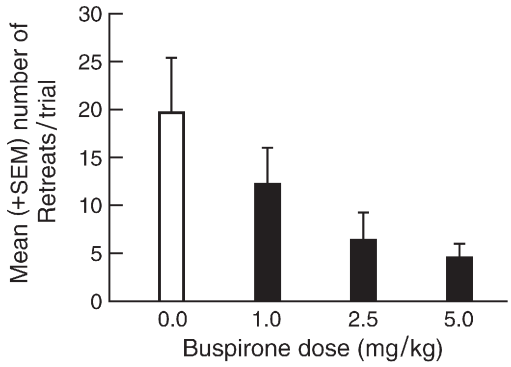

Fig. 1. Mean (+SEM) number of retreats (a measure of approach–avoidance conflict) exhibited by a single group of rats running an alley for IV cocaine and pretreated with one of four doses (0.0, 1.0, 2.5 and 5.0 mg/kg IP) of the 5-HT_{1A} partial agonist, buspirone. As described in the text, the 0.0 mg/kg condition represents the mean performance of the animals across three vehicle trials that occurred on the day/trial immediately preceding each buspirone challenge. Injections administered were IP 30 min prior to a single runway trial. The 2.5 and 5.0 mg/kg doses, but not the 1.0 mg/kg dose of buspirone reduced retreat frequency relative to saline/vehicle control levels.

and 5.0 mg/kg doses of buspirone is depicted in Fig. 1. Since the experiment employed a within-subjects design, it was important to run vehicle control trials (0.0 mg/kg dose) on the day prior to each of the three buspirone trials. A repeated measures one-way ANOVA computed on the data collected during these 3 days confirmed that there were no shifts in baseline/vehicle performance as the experiment progressed ($F(1,5)=1.23$, $p>.05$). As a result, and to simplify the subsequent data analysis, a single vehicle score (the mean number of retreats exhibited across the three vehicle trials) was computed for each animal and the group mean used to depict the "vehicle" performance in Fig. 1. A repeated measures one-way ANOVA was then computed on the data depicted in Fig. 1. This analysis yielded a statistically significant effect for dose ($F(1,5)=7.58$, $p=.04$). Post-hoc comparisons of each dose to the 0.0 saline condition were computed using a limited number (3) of repeated measures *t*-tests. Although *a priori* predictions about buspirone's effectiveness to reduce retreat behavior permitted the use of one-tailed tests (Winer, 1971), a more conservative two-tailed test was employed here to control for the small elevation in alpha error resulting from the computation of three such comparisons. These tests revealed that the low dose of buspirone was marginally effective at reducing retreats ($t(5)=3.59$, $p=.06$), while the middle and high doses were significantly different from saline ($t(5)=2.76$, $p=.04$ and $t(5)=2.86$, $p=.036$, respectively).

To provide a sense of the qualitative difference between the runway behavior of animals on saline and buspirone trials, a spatiotemporal record of a representative animal is provided in Fig. 2. Each record is a pictorial representation of the same rat's behavior during two trials (the figure was created by custom software using the real-time data derived from the infrared sensors that line the runway). The left panel of the figure depicts the animal running for IV cocaine and pretreated with 0.0 mg/kg; the right panel shows the runway behavior of the same animal on the next trial/day, a trial in which the subject was pretreated with the intermediate 2.5 mg/kg dose of buspirone. The abscissa of each graph represents real time during a single trial, while the ordinate represents the rat's location in the runway with location "1" being just outside the start box door and location "10" just outside the goal box door. As one can see from the figure, the saline-treated rat approaching the goal box associated with IV cocaine administration exhibited numerous approach and avoidance behaviors (represented as the "peaks" in the chart), before finally entering the goal box approximately 15 min into the trial (left panel). This same animal, when pretreated with buspirone (right panel) made far fewer retreats and entered the goal box within 5 min.

4. Discussion

Animals traversing a straight alley for a reward of IV cocaine develop a unique and persistent pattern of approach–avoidance

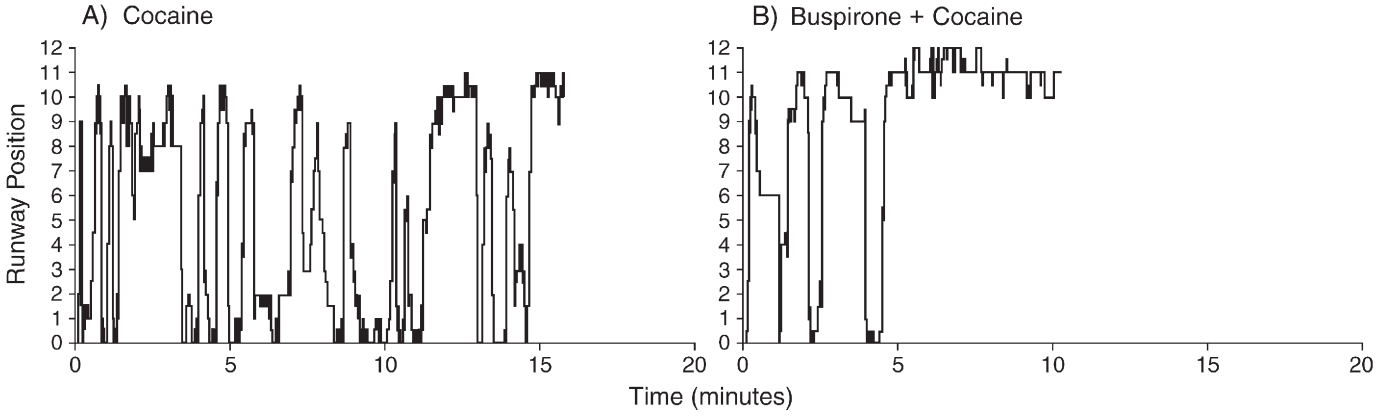

Fig. 2. Spatiotemporal records of a single representative animal running the alley for IV cocaine on a trial in which it was pretreated with either IP saline (left Panel A) or the intermediate 2.5 mg/kg dose of buspirone (right Panel B). The *x*-axis of each panel represents within-trial time (min), and the *y*-axis represents the location of the animal within the runway during the trial. Location 1 corresponds to the area just outside the start box of the alley and location 10 corresponds to the place just outside the goal box entry. The lines therefore represent the paths that the animal took in the runway before entering the goal box during two cocaine-reinforced trials — one following pretreatment with saline and the other following buspirone pretreatment. Approach–avoidance behavior is easily identified by the jagged peaks in the graphs — i.e., stops in approach behavior followed by retreats back toward the start box. Buspirone dramatically reduced this approach–avoidance conflict behavior.

behavior. Animals run quickly to the threshold of the goal box, stop, and then run just as quickly back to the start box. This retreat behavior develops over repeated trials and eventually comes to be repeated several times during each trial before the animal eventually enters the goal box and receives its cocaine infusion. The observation of retreats in the current study again confirms prior reports from our laboratory describing this behavior in cocaine-reinforced animals (e.g., Ettenberg and Geist, 1991; Guzman and Ettenberg, 2004; Knackstedt and Ettenberg, 2005; Raven et al., 2000). Note that this approach–avoidance behavior is unique to cocaine and has not been observed in animals running the alley for IV heroin (Ettenberg and Geist, 1993), oral ethanol (Czachowski, 1998), food (Ettenberg and Camp, 1986a), water (Ettenberg and Camp, 1986b), or access to sexual partners (Lopez et al., 1999). In fact, the qualitative nature of the runway behavior observed in cocaine-reinforced animals is most similar to that of hungry animals approaching a goal box associated with food plus mild footshock (Geist and Ettenberg, 1997). Indeed, as we have previously reported (e.g., Ettenberg and Geist, 1991; Raven et al., 2000) and as predicted by conflict theory (e.g., Miller, 1944), the location of the retreats are not spread randomly throughout the alley but occur in close proximity to the "choice" point, at the entry to the goal box (see Fig. 2). Additionally, it should be noted that while the animals are taking many minutes to enter the goal box, they are not running slowly. As the near-vertical slopes of the curves in Fig. 2 indicate, the animals are approaching quickly and then retreating just as quickly — a result that is again consistent with the view that retreats represent true approach–avoidance conflict that is presumably fueled by concurrent positive associations with the goal box that draw the animal near, and negative associations that push the animal away.

It has been demonstrated that 5-HT_{1A} receptor activation can produce an inhibition of spontaneous locomotor activity, and that this receptor subtype plays an important role in modulating the stimulant/locomotor response to cocaine. (e.g., Carey et al., 2005a,b; Muller et al., 2004). Others have suggested that buspirone might have sedative side-effects related to its putative antagonist actions at dopamine D2 receptors (e.g., Cervo et al., 2000). As a result of such findings, one might hypothesize that the reductions in behavior observed during buspirone challenge were in some way a consequence of the drug's inhibitory actions on motoric capacity. While the current results cannot rule out such a possibility, this view seems unlikely for several reasons. First, as indicated above, the authors saw no evidence of any buspirone-induced behavioral incapacitation in our animals. The slopes of the curves in Fig. 2 show no slowing during buspirone treatment and indeed while some investigators suggest that the drug interferes with motor capacity, others using comparable doses to those employed here, have reported that buspirone either has no incapacitating effects or produces motoric stimulation (e.g., Mignon and Wolf, 2002; Pokk and Zharkovsky, 1998; Evenden, 1994). It can also be that in a test requiring but a single runway trial per day, the motoric load or requirements for the animal are sufficiently low to mask any incapacitation that the drug might have. Whatever the explanation, there was no evidence of drug-induced "slowing" in the current study. Finally, and perhaps most importantly, the dependent measure employed in the current study (retreats) is a rate-independent behavior. The speed with which an animal approaches the goal box would understandably be altered by treatments that alter motoric capacity — but there is no *a priori* reason to believe, nor any evidence to suggest, that the location in the alley where the animal stops and turns back toward the start box is in any way affected by alterations in the motoric capacity of the subject. In our view, the most parsimonious explanation for the current results is that buspirone reduced the approach–avoidance conflict of rats approaching a goal box with which it has concurrent positive and negative associations. In that context, the present results are most comparable to those we previously observed when animals were pretreated in the same behavioral paradigm with the more traditional anxiolytic agent, the benzodiazepine, diazepam (Ettenberg and Geist, 1991).

The current findings are also consistent with clinical reports that buspirone can serve as an effective alternative to benzodiazepines in clinical treatments for general anxiety (Apter and Allen, 1999; Argyropoulous et al., 2000; Bohm et al., 1990; Fulton and Brogden, 1997; Rakel, 1990). Buspirone has also been used successfully as a prophylactic in a subset of migraine patients suffering from concurrent anxiety disorders (Lee et al., 2005), and in the treatment of those alcoholics experiencing co-morbid anxiety disorders (Cornelius et al., 2003; Malec et al., 1996). In the human research laboratory, buspirone decreased the physiologic reactivity (i.e., changes in skin conductivity) of healthy human males presented conditioned and unconditioned aversive stimuli (Bond et al., 2003; Hellewell et al., 1999).

As pointed out in the Introduction, confirmation of buspirone's anxiogenic response in animal studies has been less consistent. Particularly relevant to the current results is a report by Paine et al. (2002) who measured the effects of buspirone on the anxiogenic response to cocaine in an elevated plus maze. These investigators reported that buspirone failed to shift the anxiogenic response to either the direct administration of cocaine, or to the effects present 48 h into withdrawal from chronic cocaine. We note, however, that the maximum dose employed by Paine et al. (2002) was 1.0 mg/kg, a dose that similarly failed to produce an anxiolytic-like action in the current study. It would seem that a larger dose is required to shift the behavioral anxiogenic response of cocaine-treated animals. In other studies, buspirone appears to be less effective and/or less consistent than more traditional anxiolytic compounds in behavioral test paradigms employing shock-induced conflict/anxiety (e.g., Benvenga and Leander, 1996; Martin et al., 1993; Meneses and Hong, 1993; Sanger, 1990; Witkin and Perez, 1989). The results are more promising when other tests are employed. For example, buspirone has been shown to reduce thigmotaxic behavior (the tendency to hug the walls of an open field and avoid open spaces — a behavior sensitive to other anxiolytic agents; Angrini et al., 1998; Simon et al., 1994), to increase the time spent in the open arms of an elevated plus maze (Chang and Liao, 2005), to decrease the fear-potentiated startle response to a loud tone presented during an aversive CS (Risbrough et al., 2003), to reduce the avoidance of aversive brightly illuminated environments (Costall et al., 1988), and to

reduce ultrasonic vocalizations associated with anxiogenic affective states (Jelen et al., 2003). Such results are consistent with the general notion that 5-HT systems play an important role in the modulation of anxiety (e.g. see reviews by Abrams et al., 2005; Argyropoulous et al., 2000; Eison and Eison, 1994; Graeff, 2002; Griebel, 1995) and more specifically with the view that stimulation of presynaptic 5-HT_{1A} autoreceptors produces an anxiolytic-like action (e.g., Dekeyne et al., 2000; Koek et al., 1998; Millan et al., 1997; Schreiber et al., 1995).

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