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Lobeline Attenuates Progressive Ratio Breakpoint Scores for Intracranial Self-Stimulation in Rats

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Abstract

The alkaloid lobeline inhibits the function of vesicular monoamine and dopamine transporters and diminishes the behavioral and neurochemical effects of nicotine and amphetamines. In the present study, we examined the interaction of systemic administration of lobeline on breakpoint scores on a progressive ratio (PR) schedule of intracranial self-stimulation (ICSS) of the medial forebrain bundle (MFB). Rats were run in two 30 min sessions, separated by a 10 min timeout period. At the end of the first session, each rat was injected with either 0, 0.5, 1.0 or 2.0 mg/kg (i.p.) lobeline. Positive controls known to suppress and to augment ICSS responding included the adrenergic antagonist prazosin (0, 0.5 and 2.0 mg/kg, i.p.) and the psychostimulant cocaine (0, 1.25, and 5.0 mg/kg, i.p.). Analyses of changes in average PR breakpoint scores between the 2 sessions revealed that lobeline significantly suppressed PR scores at doses of 0.5, 1.0 and 2.0 mg/kg, as did 0.5 mg/kg and 2.0 mg/kg prazosin. These changes are unlikely to reflect motoric effects of these drugs inasmuch as neither lobeline nor prazosin alter locomotion at these doses. In contrast, PR breakpoint scores were significantly increased at 5.0 mg/kg cocaine, a dose that is sufficient to elevate locomotion in the rat. These results are consistent with the view that lobeline modulates brain reinforcement processes.

Keywords

Nicotinic receptors; Prazosin; Cocaine

Multiple behavioral assays can be used to index abuse potential [1-3] including the capacity of a drug to induce hyperlocomotion [4] and the capacity to induce conditioned place preference [5]. Rats will self-administer drugs such as cocaine or amphetamine into their vascular system [6]. Such drug infusions are thought to act on the neural substrates of reward. Electrodes placed along the path of the medial forebrain bundle (MFB) will support intracranial self-stimulation (ICSS) [7] and drugs of abuse are known to reduce the threshold current required to support ICSS [4,8,9]. Additionally, drugs of abuse are known to elevate progressive ratio (PR) responding for ICSS [10,11]. The latter types of studies are important in that a PR schedule, relative to a continuous reinforcement schedule, may be more sensitive to changes in reward engendered by neurotransmitter receptor antagonism [12].

The alkaloid lobeline is derived from *lobelia inflata* [13]. Lobeline attenuates the hyperactivity induced by methamphetamine in rats and diminishes methamphetamine self-administration in rats [14-16]. The aforementioned results suggest that lobeline may function as a therapeutic tool for the treatment of methamphetamine abuse. Inasmuch as the impact of lobeline on ICSS responding has not been previously reported, the present study considered the impact of

lobeline on breakpoints on a PR schedule of ICSS reinforcement. In this paradigm, the response requirement for reinforcement is increased systematically within a 30 min session [17]. Following completion of the first session, each rat was injected (i.p.) with either vehicle, 0.5, 1.0, or 2.0 mg/kg lobeline and changes in breakpoints were compared to the preinjection baselines. An additional group of rats were run as positive controls that were treated with 0, 0.5, or 2.0 mg/kg prazosin and then tested with the psychostimulant cocaine at doses of 1.25 and 5.0 mg/kg. Prazosin is an antagonist of α_1 -adrenoceptors known to attenuate the capacity of cocaine [18-22] and of amphetamine [19,20,23] to increase locomotion in rats whereas cocaine is a psychostimulant known to alter responding for ICSS [24].

General Methods

Animals

The animals were 15 adult male Sprague-Dawley albino rats (Harlan Industries, Houston, TX) weighing between 300–325g at the beginning of the study. The animals were housed individually in standard plastic rodent cages and were allowed a 1-week adaptation period prior to the onset of behavioral testing in order to acclimate them to daily handling and colony maintenance procedures. The animal holding room was maintained at $23 \pm 1.0^\circ \text{C}$, with a 12:12 L: D lighting schedule (lights off at 10:00 h). The rats were provided with continuous access to tap water and rodent chow pellets (Teklad) except as described in the testing procedures. The procedures of the study were approved by the Texas A&M University Institutional Animal Care and Use Committee.

Drugs

Cocaine solutions were prepared by dissolving cocaine hydrochloride (HCl: a gift provided by Dr. Kevin Gormley of the Basic Research Division of NIDA) into 0.9% saline at concentrations of 1.25 or 5.0 mg/ml. Prazosin solutions were prepared by dissolving prazosin HCl (Sigma Chemical, St. Louis, MO) into saline at concentrations of 0.5 or 2.0 mg/ml. Cocaine and prazosin solutions were calculated as the weight of the salt molecule in 1 ml of filtered saline solution. Lobeline was prepared as the weight of the base molecule (0.5, 1.0, or 2.0 mg) in 1 ml of filtered saline solution.

Surgical Procedures

Prior to surgery, each rat was injected (i.p.) with 0.4 mg/kg atropine sulfate (to minimize bronchial secretions), and then anesthetized using an injection (i.p.) of ketamine (Ketaset: 60 mg/kg) and sodium pentobarbital (20 mg/kg). Each rat was mounted in a stereotaxic frame and the scalp incised using sterile technique. A 2% lidocaine jelly was applied to the incised edges of the scalp. The periosteum was mechanically retracted and skull bleeding was terminated using a styptic gel (Kwik-Stop, Gimborn Pet, Atlanta, GA). A bipolar stimulating electrode with 0.125-mm wire diameter (Plastics One, Roanoke, VA; No. 303/3) was implanted into the MFB at the level of the lateral hypothalamus. The incisor bar was set at -2.7 mm, and coordinates were 3.2 mm posterior to bregma, 1.7 mm lateral to the sagittal suture, and 8.3 mm ventral to the skull surface. Electrodes were affixed to the skull with three skull screws and dental acrylic (Lang Dental; Wheeling, IL). The lateral edges of the scalp incision were coated with a 0.1% gentamicin sulfate ointment (E. Fougera; Melville, NY) and the ends of the incision were closed using cyanoacrylate. Following surgery, each rat was injected (i.m.) with penicillin (300,000 units each). A 7-day recovery period followed surgery, during which the rats were handled and weighed daily and had continuous access to water and food pellets in the home cage.

Apparatus

The test chamber (Cambden Instruments) was constructed of Plexiglas and stainless steel with dimensions of $28 \times 22 \times 22$ cm. Two levers were mounted on opposite sides of one wall 7 mm above the floor. Depression of the left lever was without consequence. Depression of the right lever resulted in the delivery of a 500-ms train of monophasic rectangular pulses with 1-ms pulse duration delivered from a Grass S88 stimulator (Grass Instruments, Quincy, MA) and a constant current stimulator (Model DS3) to the brain via a commutator and a flexible cable (Plastics-One). All stimulation parameters were monitored on an oscilloscope (Model 645280, Jameco Electronics, Belmont, CA).

Procedure

After the recovery period, each rat was shaped to lever press for rewarding brain stimulation on a fixed ratio-1 schedule with stimulation frequency set at 80 Hz and current intensity starting at 120 μ A. During shaping, current intensity was systematically increased by 30 μ A until a minimum rewarding current (a current sufficient to elicit lever responding) or 300 μ A was reached. The initial stimulation intensity of 120 μ A was systematically varied to locate, for each rat, the lowest intensity that maintained vigorous lever-pressing without signs of motor impairment or aversive side effects. Once lever-pressing was acquired, a PR reinforcement schedule was introduced. During the PR schedule, the session started with a 1-s train of "priming" stimulation. Each of the first four lever-presses produced a 1-s train of stimulation (i.e. reinforced on a CRF schedule). Thereafter, the response requirement increased by three responses following every fourth reinforcement delivered, resulting in the following sequence of response requirements: 1,1,1,1,4,4,4,4,7,7,7,7,10,10,10,10... [17]. The ratio requirement continued to increase until a 60-s interval elapsed without a single lever-press being emitted in which case the ratio requirement was then reset to one. Break point was defined as the ratio requirement in effect when responding ceased. Break points and number of lever presses were recorded for each rat throughout each 30-min test.

Experimental sessions consisted of two 30-min tests separated by an i.p. injection and a 10-min post-injection interval. Following initial ICSS training, each of 10 rats was tested on multiple occasions after i.p. injection of vehicle (0.9% NaCl, 1.0 ml/kg) to obtain baseline break points. These rats were then tested with 0, 0.5, 1.0 and 2.0 mg/kg lobeline. Two days of PR testing were interposed between each drug trial and lobeline doses were given in random order. For a second group of rats ($n=5$), the drug administered was prazosin HCl at doses of 0, 0.5, and 2.0 mg/kg and then cocaine HCl, at doses of 0, 1.25, and 5.0 mg/kg. For these rats, all doses were given in random order within drug condition.

Histological Analyses

At the conclusion of the experiment, each rat was overdosed with sodium pentobarbital (100 mg/kg, IP), and perfused through the heart with 0.9% phosphate buffered saline followed by 10% formalin. Further fixation in 10% formalin/30% sucrose proceeded for at least 72 h prior to sectioning each brain. Alternate 80 μ m frozen sections were stained with cresyl violet and cover-slipped for permanent storage. Coronal scans were compared to standard atlas plates [25] to verify electrode placements.

Data Analyses

For each rat and session, the total number of responses emitted and the mean break point were calculated for both the pre- and post-injection 30-min tests. The data from one rat in the positive control group was dropped as an outlier (low baseline PR values). The effects of lobeline, prazosin and of cocaine were expressed as a difference score calculated by subtracting the average post-injection break point from the average pre-injection break point of each rat in

each test session. Positive change scores indicate that PR scores declined after drug treatment whereas negative change scores indicate that PR scores increased after drug treatment. The impact of drug dose on PR difference scores was assessed using one-way analyses of variance followed by Bonferroni contrasts. Differences less than 0.05 were deemed statistically significant.

Results

Figure 1 depicts the placements of the electrode tips of the rats in the lobeline and positive control groups. Figure 2 depicts the pre and post injection PR scores and the pre-post difference scores for rats after injection of 0, 0.50, 1.0 and 2.0 mg/kg lobeline. ANOVA of the baseline pre-injection scores revealed no significant differences between the dose conditions. ANOVA of the difference scores (pre-post) revealed a significant effect of lobeline dose ($F(3,27) = 3.03, p < 0.046$). Subsequent contrasts indicated that the PR difference scores for the 0.5 mg/kg, 1.0 and 2.0 mg/kg lobeline dose conditions were significantly lower than that of the 0.0 mg/kg lobeline dose condition. Figure 3A depicts the changes in average PR scores prior to and after administration of vehicle or 0.5 or 2.0 mg/kg prazosin. PR difference scores decreased after injection of vehicle but were increased after injection of prazosin. ANOVA of these data indicated a significant main effect of prazosin dose ($F(2,6) = 7.3, p < 0.025$). Post-hoc analyses indicated that the PR scores were significantly reduced after 0.5 mg/kg prazosin relative to 0 mg/kg prazosin whereas the responses after 2.0 mg/kg prazosin were intermediate to those of 0 and 0.5 mg/kg prazosin. Each of these were significantly different from vehicle control. Figure 3B depicts the changes in average PR scores prior to and after administration of vehicle, 1.25, and 5.0 mg/kg cocaine. PR difference scores decreased after injection with 1.25 mg/kg cocaine and decreased further after injection of 5.0 mg/kg cocaine. It should be noted that the data for the 5.0 mg/kg data point are not an average of multiple breakpoints during the 30 min post-injection period inasmuch as the effect of cocaine was to so profoundly increase responding that the session typically ended as each rat was still lever-pressing. ANOVA of these data indicated a significant effect of cocaine dose ($F(2,8) = 9.80, p < 0.007$). Subsequent contrasts indicated that the 5.0 mg/kg cocaine dose was significantly different from 0 mg/kg and 1.25 mg/kg cocaine, which were not significantly different.

Discussion

The major finding of the present study was that lobeline, at doses of 1.0 and 2.0 mg/kg, significantly suppressed breakpoint scores on a PR schedule of responding for ICSS in adult male rats. In this paradigm, increases in PR breakpoint scores (or decreased pre-post difference scores) are engendered by factors that generally increase reinforcement, whereas decreases (increased pre-post difference scores) are associated with factors that impair reinforcement [17]. In the present study, increased pre-post difference scores for ICSS were noted after prazosin, a drug that blocks alpha-adrenergic receptors but pre-post difference scores in the same rats were dramatically decreased by administration of cocaine.

The capacity of systemic lobeline to increase pre-post difference scores for ICSS suggests that lobeline attenuates the reinforcing properties of ICSS. This outcome is generally consistent with other studies in which lobeline has been noted to attenuate methamphetamine self-administration [14] and to reduce responding for natural reinforcers. Harrod and colleagues, for example, reported that 3.0 mg/kg lobeline significantly suppressed responding for a sucrose reinforcer [14]. Operant performance for a food reinforcer was impaired such that 1.7 and 3 mg/kg lobeline reduced operant responding with short injection-test intervals (10 min) but not longer (40 min) injection-test intervals [26]. The duration of action of lobeline is less than one hour [14], suggesting that high lobeline doses (3 mg/kg), but not lower doses (e.g., 1.7 mg/kg) impair operant performance for a natural reinforcer. In contrast, operant performance for ICSS

in the present study was significantly altered by lobeline doses as low as 0.5 mg/kg. The mechanism of action by which lobeline alters reinforcement may be related to its effects on nicotinic receptors, opiate receptors [27] and vesicular dopamine transporters [16].

Another explanation for the impact of lobeline on PR responding for ICSS is that of general motoric impairment. This explanation, however, is not compelling given that acute administration of lobeline, at doses less than 3.0 mg/kg, does not alter locomotion in rats [16, 28]. A final explanation for the present results is related to an aversive action of lobeline as suggested by the observation that lobeline will support a conditioned place aversion [29] and that lobeline, at 3.0 mg/kg, can support a conditioned taste aversion (CTA:[13]). Brief hypoactivity after lobeline would be consistent with a malaise component of lobeline function. The observation that PR performance was altered at 0.5 mg/kg lobeline, a dose that does not induce significant CTA, suggests that malaise may not account for the observed decrement in responding. Moreover, malaise per se does not necessarily uniformly suppress ongoing behavior. Lett and Harley reported that ICSS stimulation rates *increased* after administration of lithium chloride, at doses sufficient to induce CTA [30].

Prior studies strongly implicate a permissive function of $\alpha 1$ -ARs in the reinforcement associated with MFB self-stimulation [31-34]. In the present study, systemic administration of the $\alpha 1$ -AR antagonist prazosin, at doses that block cocaine-induced hyperactivity and hypophagia [22], was noted to significantly reduce breakpoint ratio scores (i.e. increase pre-post difference scores) in responding for ICSS. The impact of prazosin was not a total blockade, but rather a reduction in responding for ICSS. This profile is similar to that noted in an earlier study in which prazosin was noted to diminish FR-1 responding for ICSS [33]. One explanation of this effect is that prazosin per se alters motor function. Infusion of $\alpha 1$ -AR antagonists (e.g. terazosin) into the cerebral ventricles suppresses locomotion [35]. The present study, however, noted effects on ICSS responding using systemic prazosin at doses of 0.5 and 2.0 mg/kg; doses that do not alter basal locomotion in an activity chamber [22,36] or in swim tests of spatial learning [37]. Moreover, in the present study, cocaine at 5.0 mg/kg markedly increased PR responding for ICSS, but in other studies this dose of cocaine is at the threshold for increasing locomotion in adult male rats [38,39].

The present findings add to a growing body of literature in which antagonism of $\alpha 1$ -ARs diminishes the behavioral effects of psychostimulants such as cocaine, morphine, amphetamine, and nicotine. Prazosin has been shown to attenuate the hyperlocomotion induced by cocaine and amphetamine [19,21,22,40] and to block the locomotor sensitization induced by repeated cocaine or amphetamine administration [19,41]. In one of the few studies available regarding conditioned place preference, prazosin pretreatment attenuated the capacity of morphine to induce conditioned place preference [36]. Prazosin modulates the capacity of tranlylcypromine to increase the reinforcing capacity of nicotine [42] and alters the release of dopamine within the nucleus accumbens. Collectively, these results support a permissive role for brain $\alpha 1$ -ARs in drug-induced reinforcement [1,42].

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Figure 1. Summary of electrode tip placements in brain (figures are reprinted with permission from [25]).

Figure 2.

Left axis: Mean group progressive ratio scores for the 30 min pre-injection tests (Pre: open bars) and post-injection tests (Post: black bars) after 0 mg/kg, 0.5 mg/kg, 1.0 and 2.0 mg/kg lobeline (n=10). Right axis: Mean group difference scores (Pre-Post) after 0 mg/kg, 0.5 mg/kg, 1.0 and 2.0 mg/kg lobeline are represented by a filled triangle. The vertical lines extending above each bar or symbol represent the standard error of the mean. Significant differences in PR difference scores between a drug dose and the vehicle are indicated by an asterisk (* = $p < 0.05$).

Figure 3.

Panel A. Left Axis: Mean group progressive ratio scores for the 30 min pre-injection tests (Pre: open bars) and post-injection tests (Post: black bars) after 0 mg/kg, 0.5 mg/kg and 2.0 mg/kg prazosin (n=4). Right axis: Mean group difference scores (Pre-Post) after 0 mg/kg, 0.5 mg/kg and 2.0 mg/kg prazosin are represented by a filled triangle. Panel B: Left axis: Mean group progressive ratio scores for the 30 min pre-injection tests (Pre: open bars) and post-injection tests (Post: black bars) after 0 mg/kg, 1.25 mg/kg and 5.0 mg/kg cocaine (n=4). Right axis: Mean group difference scores (Pre-Post) after 0 mg/kg, 1.25 mg/kg and 5.0 mg/kg cocaine are represented by a filled triangle.