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Bromocriptine, a D_2 Receptor Agonist, Lowers the Threshold for Rewarding Brain Stimulation

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KNAPP, C. M. AND C. KORNETSKY. *Bromocriptine, a D_2 receptor agonist, lowers the threshold for rewarding brain stimulation.* PHARMACOL BIOCHEM BEHAV **49**(4) 901-904, 1994.—Drug-induced lowering of brain stimulation reward threshold can serve as a model for the pharmacological activation of reward pathways. Here, the effects of bromocriptine, a direct D_2 dopamine receptor agonist, on reward thresholds were investigated. Bromocriptine administration resulted in the significant lowering of threshold levels in all test animals, suggesting that this agent can activate the same reward processes as do abused substances such as cocaine and morphine.

Self-stimulation Dopamine agonist ICSS

IT has been proposed, based on the premise that chronic cocaine use can lead to a state of hypodopaminergic activity within the brain, that the dopamine agonist bromocriptine may be of value in the treatment of cocaine dependence (3). Although it remains unclear as to what precisely is the role of dopamine in the development of cocaine dependence, a few studies do indicate that bromocriptine may be effective in alleviating some of the symptoms associated with cocaine withdrawal (3,4,10,25). It has been reported, for example, that bromocriptine treatment reduces the craving for cocaine in abstinent individuals (4), and that it decreases the intense desire for cocaine in experienced cocaine users in the period immediately following the administration of this agent (10).

Bromocriptine is an ergot alkaloid that acts selectively on dopamine D_2 receptors (11). Pretreatment with this agent has been shown to reduce levels of intake of self-administered cocaine in a dose-dependent manner (9). This finding suggests that bromocriptine interacts with the pathways involved in mediating cocaine's reinforcing effects, as do results that indicate that an injection of bromocriptine will reinstate responding for cocaine in animals in which cocaine self-administration had been extinguished (26). The observations that both monkeys (27) and rats (29) will self-administer bromocriptine are indications that this agent can activate reward processes through its own actions.

Abused substances such as cocaine (6), *d*-amphetamine (5), and morphine (15), which produce euphoric states in human subjects, have been found to lower thresholds for rewarding brain stimulation in animals. This enhancement of the sensitivity of animals to brain-stimulation reward (BSR) may be a direct reflection of the activation of reward processes by pharmacological agents. Some findings suggest that bromocriptine can facilitate the effects of rewarding brain stimulation. Rates of responding for electrical BSR delivered to the substantia nigra have been shown to be significantly increased above baseline levels in female rats treated with bromocriptine as was wheel-running activity (24). The administration of bromocriptine in animals with 6-hydroxydopamine lesions of the substantia nigra restored BSR response rate to near prelesion levels (2). Whether or not the increases in rates of responding for BSR in these experiments were definitely due to the effects of bromocriptine on reward processes is unclear because they may be attributable to the actions of this drug on motor systems associated with nigrostriatal pathways.

In this investigation, the effects of bromocriptine on the threshold for rewarding brain stimulation were determined.

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Threshold determinations were made using a rate-independent method that allows for the discrimination of drug effects on reward processes from those on motor system activity.

METHOD

Bipolar stainless steel electrodes (0.13 mm in diameter and insulated at the tips) were stereotaxically implanted bilaterally in the lateral hypothalamic region of the medial forebrain bundle (MFB-LH) of four male F-344 albino rats (300 g), (Charles River Laboratories). Surgical anesthesia was produced by systemic administration of xylazine (13 mg/kg) and ketamine (87 mg/kg). MFB-LH coordinates were 4.0 mm posterior to bregma, 1.4 mm lateral from the midline suture, and 8.5 mm ventral to the skull surface. Behavioral testing was begun approximately 1 week after surgery. Animals were maintained on a 12 L : 12 D cycle, tested during light cycle, housed individually in stainless steel cages, and had ad lib access to food and water.

The electrode that produced appetitive behavior at the lowest current intensity and had the least or no motor artifact was used in this experiment. Rats were trained and tested in a plastic chamber (20 × 20 × 35 cm). A wheel manipulandum was located within one wall of the test chamber. Immediate delivery of a stimulation occurred when the wheel was rotated one-quarter of a turn. A constant current stimulator (Sunrise Systems, Pembroke, MA) was used to deliver the biphasic symmetrical pulses. Each stimulus consisted of a 500-ms train with a pulse width of 0.2 ms and a delay of a 0.2 ms between the positive and negative pulses at a frequency of 160 Hz.

Thresholds were determined by a rate-independent, discrete trial procedure involving the use of discrete trials systematically presented over a range of stimulus intensities. The threshold method has been extensively described elsewhere (5,6,13,14).

Rats required approximately six 1-h training sessions to learn the task and approximately four additional sessions for the establishment of a stable threshold level, whereupon vehicle injections were begun. Animals were tested with vehicle injections for 5 days before drug administration was initiated. At least 72 h were allowed to elapse between drug treatment days.

Animals were injected intraperitoneally with either vehicle or bromocriptine (Sigma Chemical Co.). Doses of bromocriptine ranged between 4–16 mg/kg for three of the test animals and between 2–16 mg/kg for the fourth. Postinjection sessions were started 2 h following the administration of either vehicle or drug. All injections were given in a volume of 1 ml/kg of body weight. Bromocriptine and an equal quantity of tartaric acid were dissolved in a few tenths of a milliliter of 95% ethanol solution. The solution was brought to volume with distilled water. The final concentration of ethanol was 9.5% for every concentration of bromocriptine prepared except the 16 mg/ml solution, which had an ethanol concentration of 13.7%. Vehicle injections consisted of 4.5% ethanol with 0.8% tartaric acid in distilled water. Fresh bromocriptine solutions were prepared on each test day. The lower concentration of ethanol was used in vehicle solutions to prevent the local irritant and CNS effects that can result from chronic alcohol administration. The highest dose of ethanol administered during any test session in this study did not exceed 110 mg/kg. Behavioral testing in this investigation was not begun until 2 h after the injection of either bromocriptine or vehicle. Using the same threshold procedure as in this experiment, we have found that the significant effects were found only at doses of 1.0 g/kg or above and during the first 30 min after ethanol administration (19).

Data Analysis

Threshold values were calculated for both the preinjection and the postinjection sessions, with the difference between the two scores taken as the dependent measure (post–pre). These difference scores were transformed to standard scores (z-scores) based on the mean and standard deviation of the difference scores for all saline days. A minimum of 20 control scores for each animal were used in determining each z-score value. For an individual animal, a z-score of ± 1.96 or greater (95% confidence limits) was preselected as the level of significance.

Histology

At the completion of the experiment, the animals were killed with an overdose of pentobarbital and perfused intracardially with saline followed by formalin. The brains were subsequently removed from the skull, fixed, embedded, and sliced at 40 μ. Mounted sections were stained with cresyl violet and Luxol fast blue and examined under a light microscope to determine the placement of the electrode tips.

RESULTS

The mean of the mean presaline thresholds for each animal was 45.5 μA. The mean of the mean post minus presaline difference was 3.5 μA and the mean of the individual standard deviation used to compute z-scores was 5.8 μA. Z-scores of 0, −1, −2, and −3 were approximately equal to 49.0, 43.2, 37.4, and 31.6 μA, respectively.

Treatment with the highest dose of bromocriptine, 16 mg/kg, produced significant reward threshold lowerings, a z-score greater than 2 (95% confidence limits) in all four rats. The mean difference score at this dose (Fig. 1) was found, through use of a paired *t*-test, to significantly differ from the mean score obtained for saline treatment, $t(3) = 23.7$, $p = 0.002$. Brain-stimulation reward thresholds were significantly lowered in three of the test animals after the administration of a 12 mg/kg dose, but the difference between the mean z-score

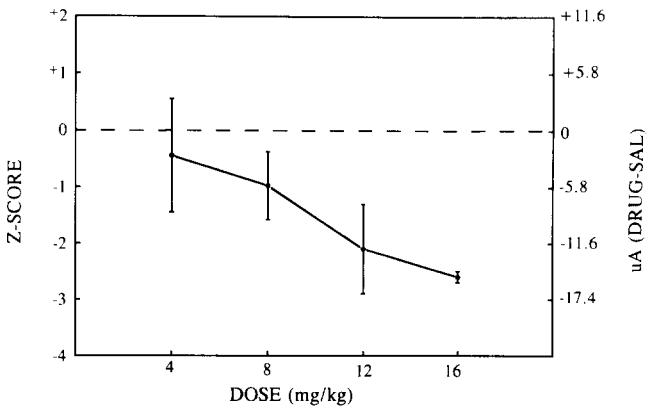

FIG. 1. Mean ± standard error z-score changes in threshold for saline treatment (z-0) for rewarding brain stimulation as a function of dose of bromocriptine. A z-score ± 1.96 indicates the 95% confidence limits. The right hand ordinate indicates corresponding changes in μA.

obtained for this dose and mean value obtained for saline administration was determined to only approach significance, $t(3) = 2.41$, $p = 0.09$. In one of the animals, bromocriptine significantly lowered the reward threshold after administration of a 4 and 8 mg/kg dose.

Treatment with bromocriptine frequently resulted in marked increases in animals' locomotor and exploratory activity. Analysis of the relationship between each animal's responses and current levels indicated that all animals were under stimulus control during drug test sessions, i.e. the slope of the regression line for probit correct responses vs. the log of current intensity was always found to be significantly greater than zero.

Histological analysis revealed that all electrode tips were placed into the caudal aspect of the lateral hypothalamus, with the electrode tips of three of the animals located medial to the MFB and inferior to the MFB for the remaining animal.

DISCUSSION

Bromocriptine was found in this investigation to lower the threshold for brain-stimulation reward (BSR), a result that is in accord with the results of self-administration studies that suggest that this agent can directly activate reward processes (27,29). The finding that a dopamine D_2 receptor agonist such as bromocriptine can enhance the effects of rewarding brain stimulation is also consistent with evidence that indicates that dopamine D_2 receptors exist in association with the pathways activated by stimulation reward. It has been demonstrated that a correlation exists between the affinity of neuroleptics for D_2 receptors and their potencies as blockers of responding for rewarding stimulation (7). Infusion of the selective D_2 receptor antagonist spiroperidol into the nucleus accumbens was found to reduce BSR response rates (18), as did systemic administration of the highly selective D_2 receptor antagonist raclopride (20). Treatment with pimozide, also a selective D_2 receptor blocking agent, raises the threshold for BSR at doses that did not impair the performance abilities of the animals (1).

Intensive sessions of cocaine self-administration have been reported to lead to an elevation of stimulation reward threshold levels (16,17). This elevation of threshold levels was reversed by the administration of bromocriptine at a dose that had no effect on the BSR thresholds of drug-naive animals (17). It has been suggested that this reduction in threshold may be related to a bromocriptine-induced reduction in post-cocaine anhedonia. The lowering of reward threshold in animals pretreated with cocaine by low doses of bromocriptine may also involve, however, the activation of reward processes in animals that have become sensitized to the effects of bromocriptine. The chronic administration of cocaine may cause dopamine autoreceptors in the nucleus accumbens to become subsensitive and so may allow for the enhanced stimulated release of dopamine from mesolimbic terminals (28) and may also result in a transient increase in dopamine D_2 receptor densities in the nucleus accumbens (8,12,21), an area implicated in the mediation of the rewarding actions of cocaine (23). If similar changes were to occur in the nucleus accumbens following intensive periods of cocaine exposure, then the potency of bromocriptine as a reward system activating agent might increase.

Whether or not the actions of bromocriptine on reward processes is in any way connected to the effects observed in clinical studies in which low doses of bromocriptine are used to treat cocaine dependence is not presently clear. The administration of bromocriptine to dependent subjects has not been found to result in euphoria or other pleasurable sensations (22). Bromocriptine has not been shown, thus far, to potentiate the euphoric effects of cocaine (22), and a few subjects have reported that these effects are blocked by bromocriptine treatment (24). There is, at present, little evidence that suggests how cocaine-induced dysphoria and compulsive drug-seeking behavior and possible disruptions in the functioning of dopaminergic systems located within reward pathways might be related to one another.

In summary, both the self-administration and brain stimulation reward models of drug reinforcement indicate that bromocriptine can produce its own rewarding effects similar to those that result from the administration of abused substances in the psychomotor stimulant and opioid classes. The precise actions of the low doses of bromocriptine used in the treatment of cocaine dependence, however, remain to be elucidated.

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