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Evaluation of the Discriminative Stimulus and Reinforcing Effects of Sertraline in Rhesus Monkeys

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VANOVER, K. E., M. A. NADER AND W. L. WOOLVERTON. *Evaluation of the discriminative stimulus and reinforcing effects of sertraline in rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **41**(4)789–793, 1992.—Rhesus monkeys (N = 4) were allowed to self-administer cocaine (0.03 mg/kg/injection) under a fixed-ratio 10 (FR 10) schedule during daily 2-h experimental sessions. When responding was stable, a variety of doses of sertraline, a serotonin reuptake blocker under development as an antidepressant, were made available for self-administration. Baseline conditions were reinstated between doses of sertraline. Cocaine 0.03 mg/kg/injection maintained high rates of injection, while total saline injections decreased to low levels within four to seven sessions. Sertraline (0.05–0.4 mg/kg/injection) did not maintain self-administration above saline levels in three of the four monkeys. In the fourth, responding was marginally above saline levels at two doses but was not systematically related to dose. In a second experiment, rhesus monkeys (N = 6) were trained to discriminate either *d*-amphetamine (0.56–1.0 mg/kg, IG) or pentobarbital (10 mg/kg, IG) from saline in a discrete-trials shock avoidance/escape paradigm. Sertraline (4.0–32 mg/kg) failed to substitute for either *d*-amphetamine or pentobarbital as a discriminative stimulus. These results suggest that sertraline is unlikely to have abuse potential in humans and is unlikely to have either *d*-amphetamine-like or pentobarbital-like subjective effects.

Self-administration Drug discrimination Sertraline Antidepressant Serotonin

SERTRALINE, (+)-*cis*-(1*S*,4*S*)-*N*-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine, is a nontricyclic compound (9) currently under development as an antidepressant in the United States. It has been demonstrated to have antidepressant-like activity in preclinical studies in animals (9) and, like several other antidepressants (e.g., fluoxetine, chlorimipramine), has been shown to be a potent blocker of serotonin (5-HT) uptake (6,9). In addition, repeated administration of sertraline has been reported to downregulate norepinephrine (NE) receptor-coupled adenylate cyclase, an effect commonly seen with clinically active antidepressants (9).

In addition to their antidepressant activity, antidepressants have been suggested to be useful for treatment of cocaine abuse (1,3,4,10). Indeed, the tricyclic antidepressant desipramine has been reported to facilitate cocaine abstinence (4). Preliminary data from case reports in humans also suggests that the 5-HT reuptake inhibitor fluoxetine may prove useful in cocaine abuse treatment (11). In rats, fluoxetine has been reported to decrease *d*-amphetamine self-administration (12, 18), while both decreases (2) and no effect (12) have been observed with cocaine-maintained behavior. In addition, sertraline and fluoxetine have been reported to decrease cocaine self-administration by rhesus monkeys, but only at doses that also decreased food-maintained responding (8). Because experimental and clinical data raise the possibility that sertraline may be useful for treating cocaine abuse, it would be important to know whether sertraline itself would be predicted to have abuse potential.

Sertraline was examined in the present experiments utilizing two animal models that have proven useful for predicting abuse potential, self-administration and drug discrimination (7,17). In one experiment, sertraline was made available for intravenous self-administration by rhesus monkeys experienced in the self-administration of cocaine. In a second experiment, sertraline was evaluated in rhesus monkeys trained to discriminate either *d*-amphetamine or pentobarbital from saline. The classification of drugs using drug discrimination paradigms in animals is highly correlated with the classification

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of drugs according to their subjective effects in humans (14,15). Therefore, responding after sertraline administration that was similar to that seen with either training drug would suggest that sertraline would have subjective effects similar to that drug.

METHOD

Experiment 1: Self-Administration

Subjects. Four adult rhesus monkeys (*Macaca mulatta*), two female (8709 and 8711) and two male (8610 and 8904), weighing between 5.2 and 10.8 kg served as subjects. Both females had previous experience with IV self-administration of cocaine. The two males were experimentally naive. To maintain stable body weights, each monkey was fed 80–130 g of Purina Monkey Chow after each session; water was available continuously. In addition, monkeys received a chewable vitamin tablet 3 days/week and occasionally received fresh fruit.

Apparatus. Each monkey was fitted with a stainless steel restraint harness and spring arm that attached to the rear of the experimental cubicle (90 × 90 × 74 cm) in which each monkey lived for the duration of the experiment. Two response levers (BRS/LVE, PRL-001, Beltsville, MD) were mounted on the inside front of each experimental cubicle 10 cm above the floor. Four jeweled stimulus lights, two red and two white, were mounted directly above each lever. Drug injections were delivered by a peristaltic infusion pump (Cole-Parmer Co., Chicago, IL) at a rate of approximately 1.0 ml/10 s. All programming and recording of experimental events were accomplished by a Macintosh II computer and associated interfaces and cumulative recorders located in an adjacent room.

Procedure. Following adaptation to the cubicle and restraint system, each animal was anesthetized with a combination of ketamine hydrochloride (1.0 mg/kg, IM) and atropine sulfate (2 mg, IM) followed in 20–30 min by halothane. When anesthesia was adequate, a silicone catheter (0.08 cm i.d., Ronsil Rubber Products, Belle Mead, NJ) was surgically implanted into a major vein (internal or external jugular or femoral veins). The distal end of the catheter was threaded subcutaneously and exited through a small incision in the back of the animal. Following surgery, the monkey was returned to the experimental cubicle and the catheter was threaded through the spring arm, out the back of the cubicle, and connected to the infusion pump. If a catheter became nonfunctional during the experiment, a new catheter was implanted, as before, following a 1- to 2-week period to allow any infection to clear.

Experimental sessions, signaled by the illumination of all white lights, were 2 h in length and were conducted 7 days a week at approximately the same time each day. During baseline sessions, animals were allowed to press the right lever to receive IV injections of cocaine (0.03 mg/kg/injection) under a schedule requiring 10 lever presses per injection (fixed-ratio 10; FR 10). During injections, the white lights were extinguished and the red lights were illuminated above the right lever. Responses occurring on the left lever were counted but had no programmed consequence. After the establishment of stable rates of responding under these baseline conditions (less than 10% variation in total number of injections per session for at least three consecutive sessions), 0.9% saline was made available for self-administration (substituted) until responding declined to low, stable levels. Subsequently, monkeys were returned to baseline conditions for one to two sessions to ensure that responding approximated previous levels. When responding was again stable under baseline conditions, a dose of sertraline was substituted for intravenous self-administration for at least the same number of sessions that had been required for responding to decline to low levels when saline was available and until there was neither an increasing nor a decreasing trend in total injections per session. Baseline conditions were reinstated between doses of sertraline. The order of doses tested was counterbalanced between monkeys.

The total number of injections averaged over the last three sessions of a sertraline substitution period was used in data analysis. These values were compared to the same values for the last three sessions of the corresponding saline substitution period. A dose of sertraline was considered a positive reinforcer in a particular monkey if the mean number of injections for the last three sessions of a test period exceeded the mean value for saline injections, and the ranges did not overlap.

Approximately 6.0 ml of venous blood was drawn from each monkey immediately after the first self-administration session of the highest dose of sertraline for analysis of plasma concentrations of sertraline. The measurement of sertraline in monkey plasma was developed and validated using a modification of an assay for sertraline in human plasma (data on file, Pfizer Pharmaceuticals). Briefly, the basic principles of the method were as follows: Sertraline (CP-51,974) and the internal standard (CP-53,631) were extracted from plasma with toluene/isopropanol. The separated organic phase was extracted with aqueous sulphuric acid. A back extraction into toluene/isopropanol was accomplished from the separated aqueous sulphuric acid (now buffered). The organic phase was evaporated under nitrogen and the evaporated material derivatized. Derivatization was followed by reconstitution of the residue in an organic solvent. Sertraline was separated from endogenous substances in the residue and quantified using gas chromatography with electron capture detection. The lower limit of quantitation was 10 ng/ml.

Drugs. Cocaine HCl (National Institute on Drug Abuse, Rockville, MD) was dissolved in 0.9% saline. Sertraline HCl (Pfizer Pharmaceuticals, Groton, CT) was initially prepared in the minimum amount of sterile water necessary to put it in solution and then diluted to appropriate concentrations with 0.9% saline.

Experiment 2: Drug Discrimination

Subjects. Six adult rhesus monkeys (*Macaca mulatta*), two female (7976, 8515) and four male (8236, 8106, 7739, and 7737), weighing between 7.0 and 11.0 kg served as subjects. All monkeys had extensive experience with the present procedure and had received other test drugs prior to the start of the present study. Monkeys were individually housed in stainless steel cages with water available continuously. Supplemental feeding consisted of 100–150 g of Purina Monkey Chow daily, at least 30 min after each session, and a chewable vitamin tablet 3 days/week.

Apparatus. During experimental sessions, monkeys were seated in a restraining chair (Plas-Labs, Lansing, MI) and placed in a wooden cubicle (175 × 85 × 65 cm) containing two response levers mounted 110 cm above the floor and a 40-W white houselight mounted on the ceiling. Two sets of white jeweled lights were above each lever. The monkey's feet were placed into shoes, the bottoms of which were fitted with brass plates through which electric shocks could be delivered. Programming and recording of experimental events were accomplished by an Aim 65 microcomputer located in an adjacent room.

Procedure. Before an experimental session, a monkey was placed in the restraint chair and administered, by gavage via a nasogastric tube, either saline (1.0–2.0 ml) or the training drug (0.56–1.0 mg/kg *d*-amphetamine or 10 mg/kg pentobarbital), followed by 1.5 ml saline to clear the tube, and returned to its home cage. Fifty-five minutes after infusion, the monkey was again placed in the restraint chair and put into the experimental chamber. The session began with a 5-min timeout, at the end of which the houselight and lever lights were illuminated (trial) and a response on one lever (the correct lever) avoided electric shock and extinguished the lights. Responding on the incorrect lever was counted and, to prevent adventitious reinforcement of response chains, started a 2-s changeover delay during which correct responses had no consequence. If a correct response was not made within 5 s following onset of the lights, electric shock (250-ms duration, 7.0-mA intensity) was delivered. If an escape response was not made, a second shock was delivered after 2 s and the trial automatically terminated. Trials were separated by a 30-s timeout during which the chamber was dark and responding had no consequence. Sessions ended after 30 trials or 20 min, whichever came first. In addition, sessions were terminated if two shocks occurred (i.e., no avoidance or escape responding) on two consecutive trials. The correct lever was determined by the infusion administered before the session. For three monkeys, the right lever was correct after drug infusions and the left lever was correct after saline infusions. This condition was reversed for the other three monkeys.

Training sessions were conducted 5 days a week according to the following schedule: SDDSS, DSSDD, where S denotes saline trials and D indicates sessions preceded by drug administration. Training of the drug–saline discrimination continued until a correct response was made on the first trial and on at least 90% of the total trials on at least seven of eight consecutive sessions, at which point testing began. Test sessions were similar to training sessions except that a response on either lever prevented shock delivery. Two different weekly sequences alternated drug, saline, and test sessions so that the first test session each week was preceded by two training sessions, one with saline and one with drug pretreatment and the second test session of the week was preceded by either vehicle or drug pretreatment (i.e., SDTST, DSTDT, where T denotes a test session). In the event that the criterion for stimulus control was not met during the training sessions, the training sequence continued.

The training dose of *d*-amphetamine (0.56–1.0 mg/kg) or pentobarbital (10 mg/kg) and saline were tested first. Following these determinations, sertraline (4.0–32 mg/kg) was administered 2 h prior to test sessions. Sertraline dose was increased until at least 90% of the trials were completed on the drug lever or the average latency to respond in a trial was increased. In addition, the highest dose of sertraline was tested at three other pretreatment times: 60, 240, and 480 min.

Approximately 6.0 ml of venous blood was drawn from each monkey immediately after the sessions testing the highest dose of sertraline for analysis of plasma concentrations of sertraline and a metabolite. Sertraline was measured in monkey plasma as detailed in the self-administration method section.

Drugs. A stock solution of *d*-amphetamine (National Institute on Drug Abuse, Rockville, MD) was dissolved in saline for administration in a final concentration of 5.0 mg/ml. Sodium pentobarbital (Sigma Chemical Co., St. Louis, MO) was diluted with 0.9% saline to a final concentration of 40 mg/ml from a stock solution (400 mg/ml) that was dissolved in a solution of sterile water:propylene glycol:95% ethanol (5:4:1). Sertraline was prepared in a solution containing five drops of Tween-80 per 10 ml sterile water. The sertraline solution was prepared daily as needed in a concentration of 4.0–32 mg/ml and administered in a volume of 1.0 ml/kg.

RESULTS

Self-Administration

Cocaine injections maintained responding above saline levels in all monkeys tested. Under baseline conditions, the mean number of cocaine injections/session ranged between 19 and 167 (Fig. 1), resulting in cocaine intake that ranged between approximately 0.6–5.0 mg/kg/session. Although there was considerable variability between monkeys in baseline drug intake, within-subjects intake was consistent over the course of the experiment. When saline was substituted for cocaine, responding declined to less than 11 injections per session, over a period of four to seven sessions, in all monkeys.

Sertraline (0.05–0.40 mg/kg/injection) did not maintain self-administration above saline levels at any dose in three of the four monkeys (Fig. 1). The fourth monkey (8610) self-administered sertraline above saline levels at two doses, 0.05 and 0.2 mg/kg/injection, but did not self-administer 0.1 or 0.4 mg/kg/injection. For 8610, average sertraline infusions per session was always below those obtained with cocaine 0.03

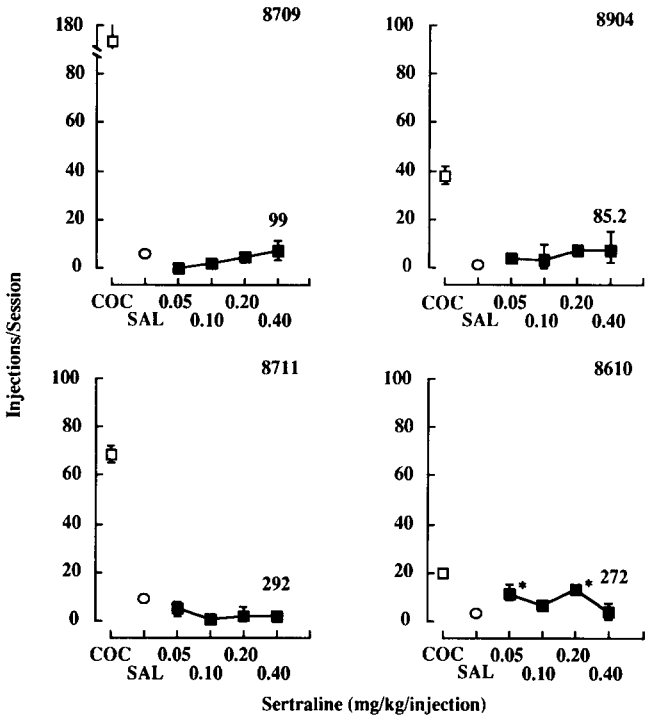

FIG. 1. Evaluation of the reinforcing effects of sertraline in monkeys experienced in the self-administration of cocaine. Each panel represents data from an individual monkey. (□), baseline cocaine (COC) self-administration; (○), saline (SAL) self-administration; (■), sertraline self-administration. Each point is the mean of the last 3 days of sertraline availability and vertical bars represent the range. For monkey 8709, the ordinate is divided to show a mean of 167 injections (range 157–183) for cocaine self-administration. * Test dose in which the total number of injections is greater than when saline was available and the ranges did not overlap. Numbers above individual data points indicate the sertraline plasma concentrations (ng/ml) after the first session of availability of the highest dose of sertraline.

mg/kg/injection. Total intake of sertraline increased with dose from between 0.02–0.57 mg/kg at 0.05 mg/kg/injection to between 0.8–2.93 mg/kg at 0.4 mg/kg/injection. In all monkeys, when 0.4 mg/kg/injection was available the number of injections during the first session were less than those seen when saline was available. During the first session of 0.4 mg/kg/injection sertraline self-administration, total intake ranged between 2.4–9.2 mg/kg, resulting in plasma sertraline concentrations between 85.2–292/ng/ml (Fig. 1).

Drug Discrimination

When saline was administered prior to test sessions, the *d*-amphetamine-trained monkeys responded exclusively on the saline lever with a mean latency of 0.31 s/trial (Fig. 2). Following the training dose of *d*-amphetamine, 100% of the trials were completed on the drug lever and mean latency increased to 0.78 s/trial. Similarly, monkeys trained to discriminate pentobarbital from saline responded virtually exclusively on the saline lever when tested with saline, with a mean latency of 0.1 s/trial. Administration of the training dose of 10 mg/kg pentobarbital resulted in 100% pentobarbital-lever responding with an increase in mean latency to approximately 0.9 s/trial. Monkeys rarely received shocks under training conditions.

Sertraline (4.0–32 mg/kg) engendered primarily saline-lever responding in all monkeys tested (Fig. 2). For 7739, sertraline (20 mg/kg) engendered approximately 93% *d*-amphetamine-lever responding the first time it was tested. However, replication of this data point resulted in primarily saline-lever responding, as did testing with higher and lower doses of sertraline. For two *d*-amphetamine-trained monkeys and two pentobarbital-trained monkeys, sertraline increased response latency above saline levels. However, these increases in response latency following sertraline were less than the increases observed following the training drug. Sertraline was tested up to 32 mg/kg in all monkeys, except 8106 (pentobarbital trained) and 7737 (*d*-amphetamine trained). Following the highest dose of sertraline tested in these two monkeys (24 and 10 mg/kg, respectively), they were observed lying in their home cage prior to testing and would not eat a sucrose pellet when offered to them; this effect on sucrose consumption was still apparent 8 h after drug administration. Sertraline dose was not increased further in these monkeys. Mean plasma concentrations of sertraline for the highest dose in each monkey administered at the 120-min pretreatment time ranged between 33 (8106, 24 mg/kg) and 312 (7737, 10 mg/kg; Fig. 2).

The discriminative stimulus effects of the highest dose of sertraline were tested at three additional pretreatment times. Sertraline did not engender drug-lever responding at pretreatment times of 60, 240, or 480 min in five of six monkeys tested (data not shown). For these five monkeys, mean plasma concentrations of sertraline at the three different pretreatment times were 157 ng/ml (range = 16–341 ng/ml), 229 ng/mg (range = 163–346 ng/ml), and 235 ng/ml (range = 113–407

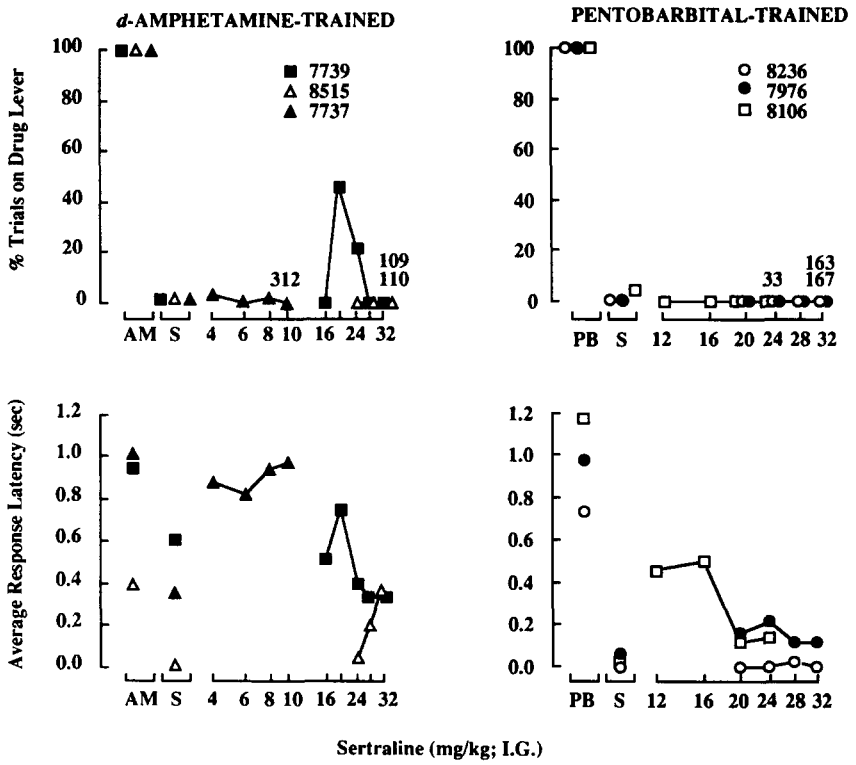

FIG. 2. Effects of sertraline in rhesus monkeys trained to discriminate 0.56–1.0 mg/kg *d*-amphetamine (AM) (left) or 10 mg/kg pentobarbital (PB) (right) from saline (S). The upper panels represent the percentage of total responses during test sessions in which drug-appropriate responding occurred, while the lower panels depict the average response latency per trial. The unconnected points at the far left of each graph represent the effects of saline and the training drug during test sessions. Each point is the mean of two or three determinations. Numbers above individual data points indicate the sertraline plasma concentrations (ng/ml) after administration of the highest dose of sertraline.

ng/ml), respectively. For 7739, the initial test of 32 mg/kg administered 480 min before the session engendered 100% *d*-amphetamine-lever responding. However, this dose engendered only saline-lever responding when tested at other pretreatment times and when retested at 480 min. The plasma concentration of sertraline after the first determination of 32 mg/kg at a 480-min pretreatment was 246 ng/ml, whereas the plasma concentration after the second determination was 473 ng/ml. Response latency for the highest dose of sertraline did not differ systematically as a function of pretreatment time.

DISCUSSION

Sertraline did not function as a positive reinforcer over a wide range of doses in rhesus monkeys experienced in the self-administration of cocaine. Responding was at or below saline levels in three of the four monkeys tested and only slightly above saline levels at two doses in the fourth monkey. That responding was less than that of saline on the first day of availability of the high dose of sertraline argues that behaviorally active doses were achieved. In addition, the plasma levels of sertraline when the high dose was tested were in excess of those seen when single doses of sertraline in the clinical range were administered to humans (50–200 mg, 12–51 ng/ml) and comparable to those observed when 200 mg was administered for 14 days (data on file, Pfizer Pharmaceutical). Although it is possible that sertraline would function as a positive reinforcer under other circumstances, the present results suggest that the compound is unlikely to have abuse potential in humans. These results also suggest that drugs whose primary mechanism of action is to increase 5-HT neurotransmission are not likely to function as positive reinforcers.

Sertraline failed to substitute for either *d*-amphetamine or pentobarbital as a discriminative stimulus. Increases of average latency to respond, as well as plasma concentrations up to 407 ng/ml, were evidence that adequate doses of sertraline were tested. Thus, it is unlikely that the subjective effects of sertraline would be similar to either pentobarbital or *d*-amphetamine. The results with *d*-amphetamine are consistent with previous reports that indirect 5-HT agonists failed to substitute for *d*-amphetamine as a discriminative stimulus in rats (5,13,16). Taken together, the present results suggest that the indirect 5-HT agonist sertraline is unlikely to have abuse potential in humans and is unlikely to have either psychomotor stimulant-like or CNS depressant-like subjective effects.

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