Drug and Alcohol Dependence, 18 (1986) 149—157

SELF-ADMINISTRATION OF METHYLENEDIOXYMETHAMPHETAMINE (MDMA) BY RHESUS MONKEYS

PATRICK M. BEARDSLEY, ROBERT L. BALSTER and LOUIS S. HARRIS

Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298-0001 (U.S.A.)

(Received February 11th, 1986)

SUMMARY

Four rhesus monkeys trained to press levers for intravenous cocaine infusions were tested with saline and (±)-3,4-methylenedioxymethamphetamine (MDMA; 3–300 μg/kg per infusion) during daily 1-h sessions. From four to over nine times more cocaine infusions were obtained than saline infusions during baseline sessions. When MDMA was substituted for cocaine, at least one dose was self-administered in 3 of the 4 monkeys at rates that exceeded the range of saline infusions. In fact, two of the monkeys self-administered a dose of MDMA at a greater rate than cocaine. These results demonstrate that MDMA can serve as a positive reinforcer for rhesus monkeys and, taken together with other preclinical behavioral studies, suggest a potential for recreational use of MDMA by humans.

Key words: MDMA — Methylenedioxymethamphetamine — Amphetamine — Self-administration — Abuse potential — Rhesus monkey

INTRODUCTION

The increasing frequency of reports of the recreational use of MDMA ('XTC' or 'ADAM') induced the United States Drug Enforcement Administration (DEA) to invoke its Emergency Scheduling Powers provided by the Dangerous Drug Diversion Control Act of 1984 to place MDMA in Schedule I under the Controlled Substances Act on July 1, 1985. A Schedule I controlled substance is a category of drugs considered to have a high abuse liability with no accepted medical use. Schedule I drugs include heroin, lysergic acid diethylamide (LSD) and MDMA's parent drug, (±)-3,4-methylenedioxyamphetamine (MDA), a potent hallucinogen with psychomotor stimulant-like properties.

Although it might be inferred from the DEA's emergency action that MDMA has high abuse liability, some psychotherapists have argued that MDMA has little potential for abuse but great therapeutic potential. For example, Greer [1] reported in an uncontrolled study involving 29 human subjects that many therapeutic benefits occurred from the administration of MDMA, including the enhancement of communication and intimacy during therapy sessions and a reduction of psychological problems, improvements in interpersonal relationships, self-esteem, and mood following these sessions. Greer [1] also concluded that, 'The potential for addiction appears to be low due to a reduction in desirable effects and an increase in side effects with frequent or excessive use.'

Little laboratory data exist pertinent to the assessment of MDMA's abuse potential. MDMA is the *N*-methyl homolog of the recreationally-used psychotomimetic, MDA. In drug discrimination studies MDA shares stimulus properties with both the hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM) and the psychomotor stimulant, amphetamine, in that DOM-trained rats generalize to the MDA stimulus [2] and (−)-amphetamine-trained rats generalize to the MDA stimulus [3]. Although (−)-amphetamine-trained rats will also generalize to MDMA [3], suggesting that MDMA has some psychomotor-stimulant-like properties, it is unlike its parent drug, MDA, in that it appears free of the DOM-like hallucinogenic stimulus effects [2]. Studies involving rhesus monkeys [4] and pigeons [5] trained to discriminate (+)-amphetamine from saline have also demonstrated that MDMA shares some of the stimulus properties of (+)-amphetamine. Locomotor activity is also increased by MDMA in mice, similar to the effects of (+)-amphetamine (G.A. Patrick, pers. commun.). Based on the drug-discrimination studies demonstrating that MDMA and (+)-amphetamine share similar stimulus properties and reports that MDMA increases locomotor activity similar to (+)-amphetamine, it might also be that MDMA has the abuse liability of a psychomotor stimulant.

One preclinical procedure that has been used to determine a drug's reinforcing properties and from which predictions of abuse potential have been made is the rhesus monkey intravenous self-administration substitution procedure. Hundreds of drugs have been evaluated using this procedure and, in general, most drugs which serve as reinforcers for animals in the substitution procedure have been also considered drugs of abuse in humans [6]. In this procedure new drugs are tested to determine whether or not they will maintain the responding of rhesus monkeys trained to lever press for intravenous delivery of a known drug reinforcer (e.g. cocaine). The results with the test compound are compared to those obtained with cocaine and with vehicle, the negative control. This procedure allows for rapid assessment of a number of doses and permits comparisons between test drugs and standards. In the present experiment MDMA was tested using this substitution procedure to see if it would serve as a positive reinforcer for rhesus monkeys trained to respond for cocaine administration.

METHODS

Animals and apparatus

Four adult male rhesus monkeys (Macaca mulatta) weighing between 7.6 and 9.8 kg were used. Monkey M-S was experimentally naive prior to the beginning of these studies; the other monkeys had previous experience in intravenous drug self-administration experiments. The monkeys were chronically housed in side their experimental cubicles (1.0 × 1.0 × 1.0 m) for the duration of the experiment. Water was continuously available through drinking spouts located at the rear of the cubicles. The animals were fed approx. 200 g of Purina Monkey Chow and a chewable multiple vitamin tablet each day following the experimental session.

A response lever was mounted at the front of each experimental cubicle on the transparent door 30 cm above the floor. A food dish was situated to the right side of the response lever. Three 2.8-W jewelled stimulus lights (a red light between two white lights) were located above the lever. Peristaltic infusion pumps (Cole-Parmer Co., Chicago, IL) delivered 10-s, 1.0-ml infusions through the catheters. Catheters travelled from the pumps through the back of the cubicles and into protective spring arms which were attached at one end to the rear of the cubicle and at the other end to a stainless steel restraint harness fitted to the monkey [7]. The activation of stimulus lights and infusion pumps and the recording of response lever depressions were accomplished by computer-based equipment located in an adjacent room.

Procedure

Surgery. The monkeys were prepared with silicone intravenous catheters (0.08 cm i.d.; Ronsil Rubber Products, Belle Mead, NJ) under phencyclidine (1.0 mg/kg, i.m.)-pentobarbital (10–20 mg/kg, i.v.) anesthesia accompanied by atropine sulfate (0.04 mg/kg, i.m.) and Cefazolin sodium (20 mg/kg, i.m.). The internal and external jugular veins and the femoral veins could be catheterized. Catheters were routed subcutaneously from the catheterized vein and exited in the mid-scapular area; they then passed through the harness and spring arm and connected to the pump. Asepsis during surgery was assiduously attempted. Occasionally, fluid samples from the catheters were cultured; when infections were present, antibiotic sensitivity tests were conducted and an appropriate antibiotic regimen employed. If a catheter became defective, it was removed and replaced into another vein after a minimum 14-day recovery period. The protocol was then resumed.

General conditions. The monkeys were tested during daily, 1-h experimental sessions. The white stimulus lights were lit at the beginning of each session. During the 10-s infusions, the white lights were turned off and the red stimulus light was illuminated. Animals obtained infusions according to a fixed-ratio-10 schedule (FR10); that is, infusions occurred for every 10 lever presses. Responses during infusions were recorded but did not count toward completion of the fixed-ratio requirement.

Baseline conditions. During baseline conditions cocaine hydrochloride was the available solution. A dose per infusion of cocaine was individually selected

for each monkey (Monkeys M-S and M432, 50 μg/kg per infusion; Monkeys M420 and M840, 33 μg/kg per infusion) which maintained stable rates of responding from session to session. Changes from a cocaine baseline condition to either a saline substitution or an MDMA substitution condition occurred following three consecutive sessions in which the number of cocaine infusions did not vary more than 20% between sessions.

Substitution procedure. All saline and MDMA substitutions lasted four consecutive sessions and were followed and preceded by a cocaine baseline condition. Following the initial cocaine baseline condition, 0.9% saline was substituted. Next, doses of MDMA (3, 10, 30, 100 and 300 μg/kg per infusion) were substituted in an irregular order. This series of MDMA doses included at least one dose which, on the first day of substitution, resulted in lower infusion rates than the average rates of infusion occurring on the first day of the two saline substitutions which thus provided some assurance that behaviorally active doses were being tested. Following the final test dose of MDMA, 0.9% saline was again tested.

Drugs. MDMA ((±)-*N*-methyl-3,4-methylenedioxyphenylisopropylamine hydrochloride) and cocaine hydrochloride were provided by the National Institute on Drug Abuse. They were dissolved in sterile 0.9% saline. Doses were calculated as the salts.

Data analyses. The number and distribution of infusions over the last three sessions of each MDMA or saline substitution condition were used in data analyses. The data from the last three sessions of all the cocaine baseline conditions were used in calculations of summarized data.

A test dose of MDMA was considered to be a positive reinforcer if the mean number of infusions exceeded the mean number of saline infusions and their ranges did not overlap. Additional evidence for whether a test dose of MDMA was a reinforcer was whether the within-session time course of the occurrence of MDMA infusions resembled that of cocaine, the positive control, or that of saline, the negative control.

RESULTS

Under baseline conditions cocaine maintained stable rates of responding which were beyond the range of saline responding (Fig. 1). At least four times more (Monkey M432) to over nine times over (Monkey M840) cocaine infusions occurred, on the average, than saline infusions. The mean amount of cocaine self-administered per 1-h session ranged from 1.73 mg/kg (Monkey M420) to 4.48 mg/kg (Monkey M432).

Figure 1 (left panels) shows the mean number of MDMA infusions obtained per 1-h session during each substitution. For three of the four monkeys (M840, M432 and M-S), at least one dose of MDMA was self-administered beyond the range of saline infusion rates. Two doses of MDMA for Monkeys M840 and M-S (30 and 100 μg/kg per infusion) and one dose of MDMA for Monkey M432 (30 μg/kg per infusion) were self-administered above the range of saline-control levels. For two of the monkeys (M840 and M-S) a dose of MDMA (30 and

100 μg/kg per infusion, respectively) was self-injected at a higher rate than cocaine. Only Monkey M420 did not self-administer any of the tested doses of MDMA. The range of MDMA test doses included behaviorally active doses as evidenced by the fact that for each monkey, fewer infusions occurred on the first day of substituting the 300 μg/kg per infusion dose (and, at times, lower doses) than occurred on the first days of saline substitution, suggesting some degree of response-rate suppression and behavioral activity.

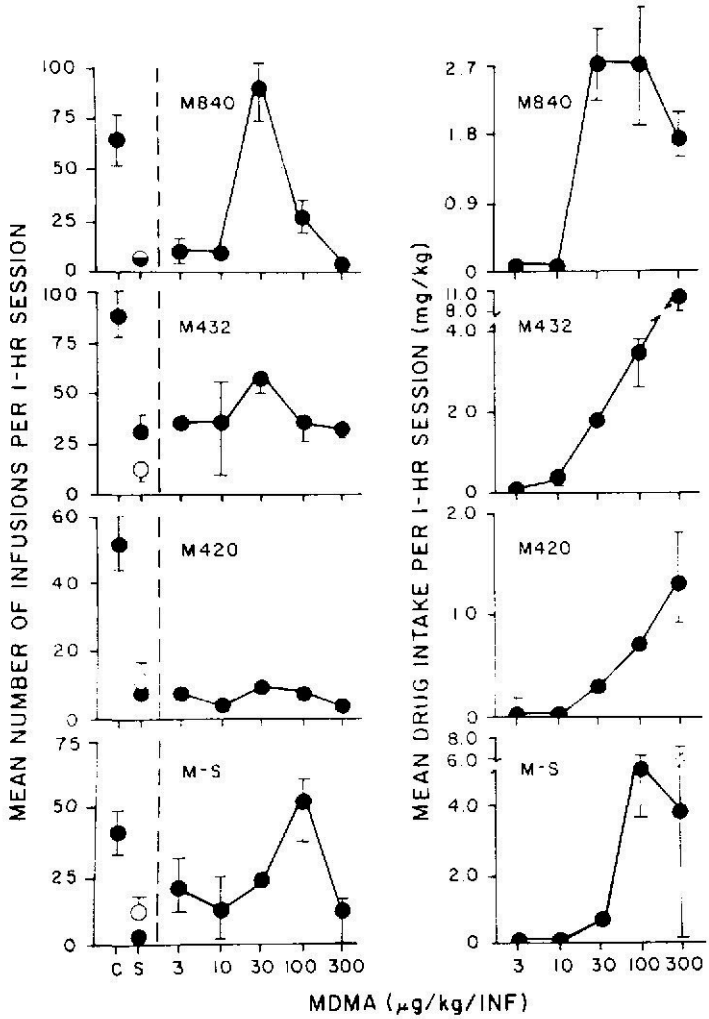

Fig. 1. Left panel: The mean number of cocaine (C), saline (S) and MDMA infusions obtained during the last three sessions of each condition for each of the four monkeys. Cocaine data points represent the mean of the last three sessions of all cocaine baseline conditions. Saline data points represent the mean of the last three sessions of the first (●) and second (○) saline substitution condition. Vertical lines through the saline and MDMA data points represent the range. Vertical lines through the cocaine data points represent the standard deviation. Right panel: Mean total intake (mg/kg) of MDMA obtained per 1-h session during the last three sessions of each substitution condition for each monkey. Vertical lines through the data points represent the range.

Figure 1 (right panel) shows that for two of the monkeys that self-administered MDMA (Monkeys M840 and M-S) the mean MDMA intake was an inverted curvilinear function of dose; at lower doses mean MDMA intake increased with increasing doses then decreased with subsequently higher doses. Monkey M432 showed a linear increase in MDMA intake with increases in dose; this monkey obtained the highest intake of MDMA of all the monkeys, self-administering over 11 mg/kg of MDMA during substitution sessions at 300 μg/kg per infusion.

Monkey M432 showed behaviorally toxic effects of MDMA immediately following the session at which he self-administered his overall greatest quantity (i.e. 11.1 mg/kg), displaying repetitive wrist flexions and stereotypic chewing-like movements, piloerection, oculomotor hyperactivity, and mydriasis. Monkey M420, which did not self-administer MDMA at any dose, increased

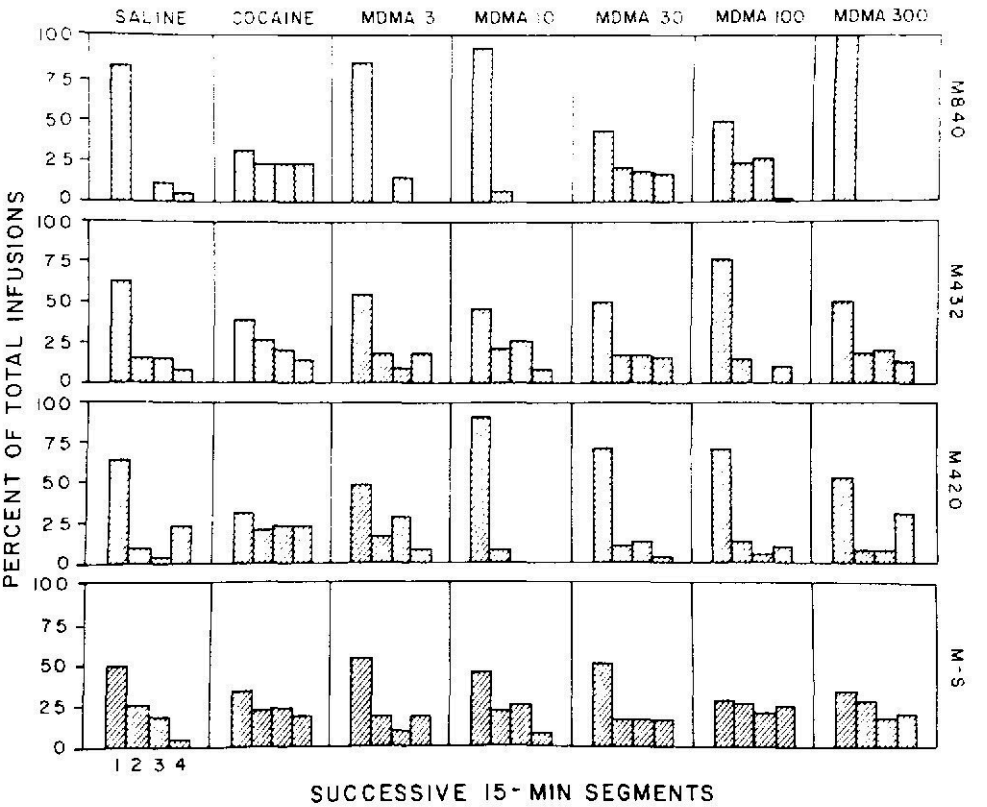

Fig. 2. The within-session distribution of saline, cocaine and MDMA infusions for each of the four monkeys. Each bar represents the mean percent of the total number of infusions obtained during each 15-min segment of the last three 1-h sessions of each condition. Bars representing saline infusions are the mean for the last 3 days of both saline substitution conditions. Bars representing cocaine infusions are the mean for the last 3 days of all cocaine baseline conditions.

his intake of MDMA with increases in dose (Fig. 1, right panel). Monkey M420, however, was only obtaining an average of 1.3 mg/kg session at 300 μg/kg per infusion when his intake was highest.

Comparisons among the patterns of responding maintained by saline, cocaine, and various doses of MDMA are shown in Fig. 2. With saline, most infusions (65% on the average for the group) were obtained during the first quarter of the substitution sessions suggesting an extinction pattern. Also indicative of extinction was the fact that for all monkeys during both saline substitutions more infusions occurred on the first day than on the fourth day of substitution (data not shown). For cocaine, however, homogenous rates of infusions generally occurred across all four quarters of substitution sessions (Fig. 2), suggesting responding was maintained by cocaine. The patterns of MDMA intake, at doses that were self-administered, were intermediate between those of saline and cocaine in that the distribution of infusions did not show the marked skewness toward first quarter responding as that of saline but the distribution was also not as homogenous as that generated by cocaine. At times during substitution of self-administered MDMA doses, more infusions occurred on the last day of substitution than on any other (data not shown) which is opposite to that which occurred with saline substitution. Doses of MDMA that were not self-administered according to our criteria (including all doses for M420) usually generated within-session patterns of intake more similar to those of saline, with the exception of the 300 μg/kg per infusion dose for M-S which generated a cocaine-like pattern of intake.

Experience with MDMA did not systematically affect rates of cocaine self-administration. For Monkeys M420 and M-S the rate of cocaine self-administration during the baseline period immediately before the first test dose substitution of MDMA was similar to the rate immediately following the last test dose substitution of MDMA (M420: 52.3 and 48.7; M-S: 38.3 and 37.6, mean cocaine infusions before and after the MDMA test series, respectively). For M840 the rate of cocaine self-administration was higher, and for M432 the rate of cocaine self-administration was lower, before the MDMA test series than after (M840: 66.0 and 49.0; M432: 72.0 and 100.0, mean cocaine infusions before and after the MDMA test series, respectively).

DISCUSSION

The results of these tests have demonstrated that MDMA can serve as a reinforcer for rhesus monkeys. Drugs recreationally used by humans are usually intravenously self-administered by rhesus monkeys; drugs that are not recreationally used by humans are usually not self-administered by rhesus monkeys [6]. Based on the present data then, one would predict a potential for recreational use of MDMA. The present data, however, are not the only preclinical data which provide evidence for an abuse potential for MDMA. Rats [3], rhesus monkeys [4] and pigeons [5] trained to discriminate (+)-amphetamine from saline respond to tests with MDMA in an

amphetamine-like manner, suggesting that some of the stimulus properties of amphetamine and MDMA are similar. Generally it is inferred that when drugs share discriminative stimulus effects they have subjective effects in common [8]. When a test drug shares subjective effects with a drug of abuse there usually is the likelihood that the test drug also has abuse potential [9]. Besides the present self-administration studies and the drug discrimination studies, others have found that MDMA stimulates motor activity in mice similar to that of (+)-amphetamine (G.A. Patrick, pers. commun.) indicating another similarity between MDMA and the highly abused drug (+)-amphetamine.

These preclinical data are compatible with the anecdotal reports of street use of MDMA. Although little definitive epidemiological data are available describing the frequency of the illicit use of MDMA, recent seizures of MDMA by the DEA, including a nearly 2-kg seizure in Miami, Florida in September of 1983, suggest some incidence of the recreational use of MDMA. Claims that MDMA has little abuse liability [1] seem not to be in accord with the sum of these data.

Because one monkey of the group (Monkey M420) did not self-administer MDMA, the group was tested in substitution tests following the MDMA experiment with one or two doses of (−)-amphetamine, to ascertain whether Monkey M420's rejection of MDMA generalized to a structurally-similar drug with known, high abuse liability, and to verify that the other monkeys would be consistent in self-administering abused psychomotor stimulants. All the monkeys self-administered (+)-amphetamine above the range of saline control. On the first day of (+)-amphetamine substitution (30 μg/kg per infusion), Monkey M432 self-administered 3.57 mg/kg during the 1-h session. In the days following this 1 day of (+)-amphetamine substitution, Monkey M432 was lethargic and appeared in ill health; he was not given further tests with (+)-amphetamine. Monkey M420, which did not self-administer MDMA, did self-administer 10 and 30 μg/kg per infusion (+)-amphetamine (mean infusions: 40.3 and 15.3/1-h session, respectively).

Occasionally, not all monkeys within a test group will self-administer a drug during substitution testing. Sometimes this occurs when the test drug has an abuse liability intermediate between drugs that are not recreationally used and those which are considered to have a very high likelihood for abuse. For instance, Balster et. al., [reported in Ref. 10] found that all monkeys self-administered morphine, a drug considered to have high abuse liability, but only half the group self-administered pentazocine, a drug considered to have liability for abuse, but less than that of morphine. Because not all the monkeys self-administered MDMA but all did self-administer (+)-amphetamine, and because the within-session distribution of infusions of self-administered doses of MDMA was generally intermediate between that of saline (the negative control) and that of cocaine (the positive control) it is possible that MDMA has an abuse liability which is less than that of cocaine or (+)-amphetamine.

Behavioral toxicity was evident in Monkey M432 after self-administering 11.1 mg/kg MDMA during a 1-h session. These toxic effects included repetitive wrist and chewing movements, piloerection, oculomotor hyperactivity and

mydriasis. Many of these toxic effects have also been reported at high MDMA doses in the dog [11]. These effects are similar to effects seen at high doses of amphetamines [12].

Proponents of the use of MDMA in psychotherapy have reported that treatments with MDMA in therapy can result in reductions of substance abuse. For example, Greer [1] reported that 14 of 28 subjects treated with MDMA subsequently decreased their use of mind- and mood-altering substances including one subject with a cocaine-using history who refrained from cocaine use for many months following treatments with MDMA. It should be pointed out, however, that these were uncontrolled studies lacking objective data. The data of the present experiment did not show a systematic relationship between rates of cocaine self-administration and experience with MDMA. For two monkeys, rates of cocaine intake were similar, for one they were higher, and for one they were lower before MDMA testing compared with after MDMA testing. The rate of self-administration of a drug of abuse may be decreased during MDMA administration because MDMA can serve as a drug-reinforcer itself, substituting for other drug reinforcers.

In conclusion, intravenous MDMA functioned as a positive reinforcer in three out of four rhesus monkeys. These data, combined with data from other laboratories showing amphetamine-like effects, suggest that MDMA has potential for abuse.

ACKNOWLEDGMENTS

This research was supported by National Institute on Drug Abuse (NIDA) Contract No. 271-81-3830 (Dr. K. Asghar, project officer). Dr. Beardsley was a post-doctoral trainee supported by NIDA training grant DA-07027. The technical assistance of Robert D. Groseclose and the secretarial assistance of Bonny T. Hopkins is greatly acknowledged.

REFERENCES

1 G.G. Greer, Personal publication, 333 Rosario Hill, Santa Fe, New Mexico, 87501, 1983, pp. 1–15.
2 R.A. Glennon, R. Young, J.A. Rosecrans and G.A. Anderson, Biol. Psychiatry, 17 (1982) 807.
3 R.A. Glennon and R. Young, Pharmacol. Biochem. Behav., 20 (1984) 501.
4 J.B. Kamien, C.E. Johanson, C.R. Schuster and W.L. Woolverton, Drug Alcohol Depend. 18 (1986) 139.
5 S.M. Evans and C.E. Johanson, Drug Alcohol Depend. 18 (1986) 157.
6 C.E. Johanson and R.L. Balster, Bull. Narc., 30 (1978) 43.
7 G.T. Deneau, T. Yanagita and M.H. Seevers, Psychopharmacologia, 16 (1969) 30.
8 D.A. Overton, in: T. Thompson and R. Pickens (Eds.), Stimulus Properties of Drugs, Appelton-Century-Crofts, New York, 1971, p. 87–110.
9 C.R. Schuster, M.W. Fischman and C.E. Johanson, in: T. Thompson and C.E. Johanson (Eds.), Behavioral Pharmacology of Human Drug Dependence, NIDA Research Monograph Series No. 37, U.S. Government Printing Office, Washington, D.C., 1981, pp. 116–129.
10 R.L. Balster and S.E. Lukas, Drug Alcohol Depend., 14 (1985) 249.
11 H.F. Hardman, C.O. Haavik and M.H. Seevers, Tox. Appl. Pharmacol., 25 (1973) 299.
12 E.H. Ellinwood, Biol. Psychiatry, 3 (1971) 25.