Pharmacology Biochemistry & Behavior, Vol. 38, pp. 897–903. Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Orally Delivered Cocaine Functions as a Positive Reinforcer in C57BL/6J Mice

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Received 30 August 1990

GEORGE, F. R., G. I. ELMER, R. A. MEISCH AND S. R. GOLDBERG. *Orally delivered cocaine functions as a positive reinforcer in C57BL/6J mice*. PHARMACOL BIOCHEM BEHAV **38**(4) 897–903, 1991.—Cocaine serves as a reinforcer across several routes of administration and species. However, whether orally delivered cocaine serves as a positive reinforcer has not been systematically established. We determined the extent to which contingent access to orally delivered cocaine would maintain lever pressing behavior in C57BL/6J mice who had a prior history of operant ethanol-reinforced behavior. The findings presented in this report demonstrate that orally delivered cocaine can serve as a reinforcer of operant behavior. A drug substitution procedure where cocaine was substituted for gradually decreasing ethanol concentrations was successful in inducing pharmacologically significant intakes of cocaine under a fixed ratio (FR) schedule of drug access. When ethanol was removed, responding for cocaine continued. As FR size was increased, proportionate increases in responding occurred except at the highest FR value. Responding maintained by cocaine significantly exceeded responding maintained by vehicle, with the mice typically consuming 6–10 mg/kg cocaine per 30-min session. The utilization of inbred strains and the procedures followed in the present studies should prove useful in determining the extent of both genetic and environmental influences on various behavioral effects of cocaine and their mechanisms of action.

Cocaine Self-administration C57BL/6J mice Fixed ratio

INTRAVENOUS (IV) injection of drugs from a number of pharmacological classes, including narcotic analgesics, sedative-hypnotics, psychomotor stimulants, and dissociative anesthetics, has been shown to reinforce operant behavior (21, 28, 43, 47). Cocaine administration in particular functions as an effective reinforcer of operant behavior across a number of species and under a wide range of conditions (17, 18, 21, 55). While most of these studies employed an IV route of delivery, other routes, including intramuscular (17), intragastric (1, 51, 54), inhalation (5,53) and oral (27) have been used.

The use of operant oral self-administration techniques has demonstrated that oral delivery of drugs from many pharmacological classes can serve as a powerful reinforcer under operant conditions in mice (4–7), rats (29, 39, 41, 42), rhesus monkeys (23, 31, 33), and baboons (24). There are, however, two common problems in establishing a drug as a reinforcer when it is delivered orally. The first is the aversive taste of many drugs of abuse, including ethanol, pentobarbital, cocaine and morphine. The second problem is the amount of delay between drug intake and the onset of the interoceptive effects that follow absorption (34). To overcome these difficulties, adjunctive drinking procedures employing limited access to food under various contingent and noncontingent conditions have been devised which facilitate establishment of orally delivered drugs as reinforcers (8, 27, 31). After these intitial training procedures, animals will drink intoxicating amounts of ethanol (8, 23, 29, 31), phencyclidine (3), etonitazine (32) and pentobarbital (33) in preference to water.

While it has been shown that animals will self-administer orally delivered cocaine under polydipsic conditions (49), the ability of oral cocaine delivery to maintain operant behavior, that is, to serve as a positive reinforcer, in laboratory animals has not been systematically established. Preliminary studies suggest that monkeys may work in an operant situation for access to cocaine contained in gum (45), and chewing of coca leaves is a common

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route of cocaine administration in humans (15,22). Recently, it has been shown that cocaine delivered orally can function as a positive reinforcer of operant behavior in rhesus monkeys (30). In addition, cocaine delivered orally has been shown in human subjects to produce reports of euphoria greater than that found with intranasal administration (50), and orally administered cocaine has been used in the experimental treatment of depressed patients (35,36). Thus while studies have shown that cocaine is pharmacologically active when delivered orally and that induction techniques can produce large intakes of this drug, it has not been systematically demonstrated that cocaine is functioning as a positive reinforcer when delivered orally.

Cocaine also produces marked behavioral effects such as decreases (11) and increases in locomotor activity (14, 37, 38, 40, 44) and changes in rates of occurrence of certain schedule-controlled behaviors (20, 46, 48). While the number of reports is limited, results from existing studies suggest that genotype is important in determining the extent of responses to cocaine (10–14, 40, 44). Thus control of genetic variation, such as through the use of inbred rodent strains (10,11), may be important in determining the relationships among various cocaine-related variables.

The primary purpose of the present research was to determine whether orally delivered cocaine could come to serve as a positive reinforcer. In these studies, we chose to use C57BL/6J mice, since other drugs such as ethanol and opioids have previously been shown to be positively reinforcing in mice from this strain (4–7, 25, 26). Thus a second purpose was to provide initial data concerning possible common factors in reinforcement behavior across abused substances from different pharmacological classes. We were interested in learning whether animals for which ethanol and opiates function as positive reinforcers would self-administer cocaine under operant conditions.

METHOD

Animals

For the self-administration experiments described below, four adult male C57BL/6J mice [Jackson Laboratories, Bar Harbor, ME (JAX)], weighing 22–25 g at the start of the present experiment (80% of free feeding weight), were used. These animals had previously served as subjects in a series of ethanol self-administration studies described elsewhere and had identical treatment histories (4–7). Animals were housed individually and given free access to tap water in their home cage for the duration of the experiment. Animals remained at 80% of their free feeding weights and received all of their daily food allowance after the session. Ad lib water was available in the home cages between sessions. All mice were maintained in a temperature-controlled room (26°C) with a 12-h light-dark cycle (0700–1900 lights on). Facilities for animal housing were fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) and the studies were conducted in accordance with the Guide for Care and Use of Laboratory Animals provided by the NIH and adopted by the NIDA.

Drugs

L-Cocaine HCl obtained from the National Institute on Drug Abuse was used in all studies. Cocaine was dissolved in tap water at room temperature. All concentrations are expressed in terms of mg/ml base.

Apparatus

The mouse operant chambers used have been described in detail previously (4). Four chambers were used for this study, each was enclosed in a sound-attenuating cubicle. A liquid reservoir was mounted on the outside of the chamber. A small muffin-type fan provided internal ventilation. During sessions, a white house light was continually lit. A lever, consisting of a balanced rocker arm designed to break an infrared beam with application of 0.5 g force, was located on a panel adjacent to the liquid delivery system spout.

In this liquid delivery system, adapted from Beardsley and Meisch (2), a brass spout is used to deliver a minute amount of liquid in response to a lick. An electronic circuit senses the small current (resistance adjusted to 5.0 megohms) traveling from the spout, through the animal's body, to the grounded cage floor. As the tongue contacts the spout tip, a solenoid valve is opened momentarily to deliver a droplet of liquid (approx. 2 μl/lick) directly onto the tongue.

In the present experiments, liquid deliveries were available under a heterogeneous chain schedule of reinforcement. Under this schedule, at the start of the session a stimulus light located above the lever was turned on. Completion of the required number of lever presses turned off the lever light and illuminated stimulus lights above the spout. These lights signalled initiation of the second component of the chain, during which each spout lick resulted in delivery of liquid onto the animal's tongue. Following the tenth lick, the spout stimulus lights were turned off, signaling completion of the chain, and the lever stimulus light was again turned on. Since the number of spout contacts available per completion of a fixed ratio schedule of lever presses was held constant at ten throughout these experiments, the reinforcement schedule will be referred to as a fixed ratio (FR) N, where N equals the number of lever presses required to activate the liquid delivery system. This system represents an effective and quantitative method for assuring oral delivery of drug solutions to the animal subject, since liquid delivery is directly into the animal's mouth following spout contact, and since continued lever pressing in the absence of spout contacts has no effect. System control, as well as data acquisition, storage, and initial analyses, were performed on Apple IIe computers located in an adjacent room.

Data Analysis

For all experiments, group designs using within subjects repeated measures analysis of variance (ANOVA) were used. Self-administration of cocaine was measured in several ways, including numbers of lever presses maintained by drug delivery and volume of liquid consumed. Where significant overall F values were obtained, post hoc comparisons were performed using Dunnett's *t*-test.

Procedure

The details of the procedure used to initiate lever pressing and drinking have been described elsewhere (4–7, 27). In the present experiments, all sessions were run 7 days/week between 1200 and 1400 hours. Operant test sessions lasted 30 min.

Experiment 1. Substitution Procedure

The procedure used to establish cocaine as a reinforcer was similar to that used in other species (31). Each condition during the entire substitution procedure was held constant for at least 4 sessions of stable behavior. Stability was defined as no significant change from the previous days' results. Baseline levels of responding were first obtained under 8% ethanol (w/v) at FR1. Once responding became stable, the ethanol concentration was

reduced to 6%, and cocaine, 0.1 mg/ml, was added to the delivered solution. The cocaine concentration was next increased to 0.2 mg/ml while the ethanol concentration remained at 6%. For the remainder of the substitution procedure, the cocaine concentration was held constant at 0.2 mg/ml while the ethanol concentration was gradually reduced. The ethanol concentration was further decreased logarithmically, in order, from 6.0% to 4.0, 3.36, 2.83, 2.38, 2.0, 1.41, 1.0 and 0% (water), with each condition held constant for at least four days of stable responding. It typically took one or two days at each condition before responding became stable thus each condition was usually presented for five or six days.

Experiment 2. Comparison of Responding Maintained by Drug Versus Responding Maintained by Vehicle at FR1

To determine if cocaine had come to function as a reinforcer, 0.2 mg/ml cocaine was tested followed by vehicle (water), then a retest at 0.2 mg/ml cocaine. Each cocaine condition was held constant for at least 4 sessions of stable behavior, whereas the vehicle condition remained in effect for 15 sessions. All sessions were run at FR1.

Experiment 3. Cocaine Responding as a Function of FR Size

The cocaine concentration was held constant at 0.2 mg/ml while the FR size was gradually increased from 1, to 2, 4, 8, 16 and 8 (retest). Each condition was held constant for four to six total days, including four consecutive stable days.

Experiment 4. Comparison of Responding Maintained by Drug Versus Responding Maintained by Vehicle at FR8

Responding at FR8 for cocaine was again tested for five sessions, followed by FR8 with vehicle (water) for six sessions, and another retest with cocaine at FR8 for five sessions.

RESULTS

Experiment 1. Substitution Procedure

Figure 1 (A,B,C) shows lever presses, cocaine intake (mg/kg) and ethanol intake (g/kg), respectively, as a function of cocaine (mg/ml) and ethanol (w/v) concentrations. At 8% ethanol, the mice made 37±6 (mean±SEM) lever presses per 30-min session, resulting in an average ethanol intake of 2.0 g/kg per 30-min session. When the ethanol concentration was decreased to 6.0% and cocaine was introduced at 0.1 mg/ml, there was no significant change in lever presses. Cocaine intake during this condition was 2.7±0.3 mg/kg. As the substitution procedure progressed, lever presses tended to increase, while ethanol intake decreased significantly, $F(10,30)=12.88$, $p<0.001$, and cocaine intake increased significantly, $F(10,30)=3.08$, $p<0.01$. As the ethanol concentration was gradually decreased, lever presses and cocaine intake remained relatively stable across ethanol concentrations of 6.0%, 4.0%, 3.36% and 2.83%, while ethanol intake decreased nearly linearly as a function of decreasing ethanol concentrations. Cocaine intake increased from 2.7±0.3 mg/kg at the 6.0% ethanol/0.1 mg/ml cocaine combination to 6.2±1.0 mg/kg at 0.2 mg/ml cocaine alone. The greatest cocaine intake, 6.4±1.3 mg/kg, occurred at the 1.0% ethanol/0.2 mg/ml cocaine combination.

Experiment 2. Comparison of Cocaine and Vehicle Responding at FR1

Figure 2 (A,B) shows lever presses and cocaine intake as a function of increasing FR size. At FR1, cocaine responding and consumption of the 0.2 mg/ml concentration did not significantly exceed that of the vehicle.

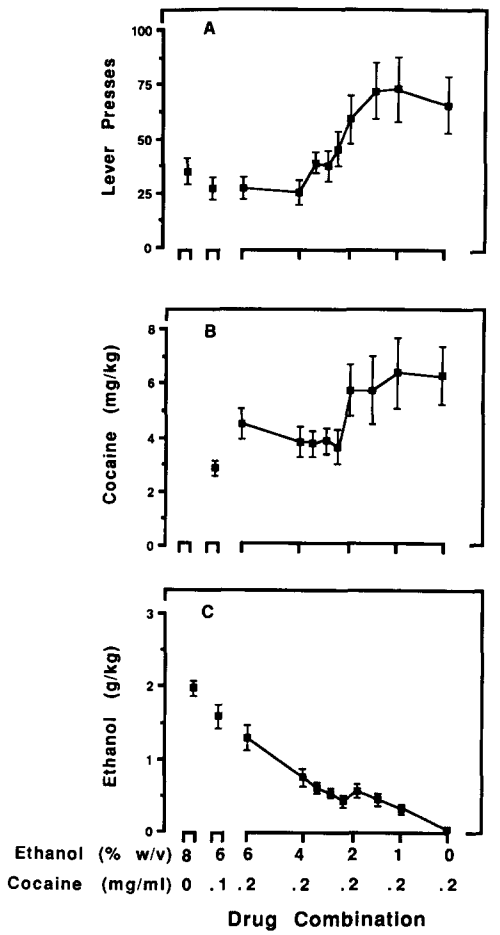

FIG. 1. Substitution procedure. A, B, and C illustrate lever presses, cocaine intake (mg/kg), and ethanol intake (g/kg), respectively, as a function of ethanol and cocaine concentrations. Each point represents the condition mean (±S.E.M.) of 4 C57BL/6J mice over a minimum of four consecutive sessions.

Experiment 3. Cocaine Responding as a Function of FR Size

At the 0.2 mg/ml concentration of cocaine (Fig. 2A,B), as the FR value increased from 1 to 8, the number of lever presses increased significantly, $F(5,15)=6.02$, $p<0.005$, and as a result, the number of reinforcement components did not significantly decrease across these FR values. When FR value was increased from 8 to 16, lever presses did not increase significantly ($t=0.36$, n.s.), resulting in a decrease in reinforcement components and cocaine intake. Figure 3 shows representive cumulative recordings of response patterns at FR1, 2, 4, 8 and 16. Greater than 80% of the responding occurred during the first 15 minutes at all fixed ratio sizes, that is, responding was negatively accelerated.

Experiment 4. Comparison of Cocaine and Vehicle Responding at FR8

Figure 2 (A,B) also shows lever presses and mg/kg intake of cocaine as a function of the experimental condition at FR8. Responding for and consumption of 0.2 mg/ml cocaine significantly

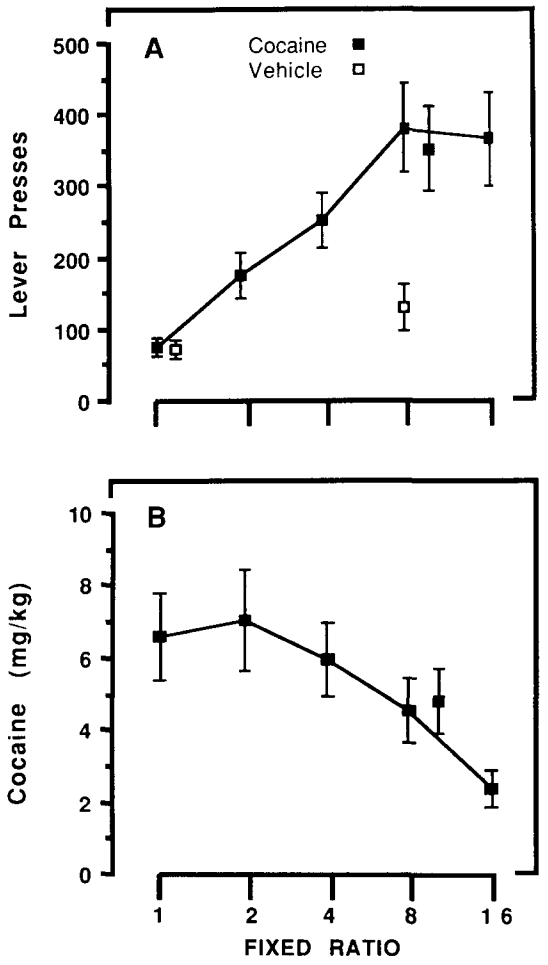

FIG. 2. Behavior maintained by 0.2 mg/ml cocaine and vehicle as a function of fixed-ratio size. A and B show lever presses and cocaine intake (mg/kg) respectively. Each point represents the condition mean (± S.E.M.) of 4 C57BL/6J mice over a minimum of four consecutive sessions.

exceeded that of the vehicle at FR8 [F(Lever Presses)(2,6) = 5.26, $p<0.05$ and F(Intake)(2,6) = 5.45, $p<0.04$]. Cocaine intake at FR8(retest) was not significantly different from that at the original FR8 test condition. Lever presses maintained by the water vehicle at FR8 did not differ significantly from responding maintained by water or cocaine at FR1. Figure 4 shows representative cumulative recordings for cocaine and vehicle at FR8. Cocaine reinforced lever pressing occurred primarily during initial portions of the session thereby producing a negatively accelerated response pattern. Some responding was maintained under the vehicle condition, but was significantly lower than and more sporadic than responding maintained by cocaine.

DISCUSSION

In the experiments reported here, the strategies successfully used previously to establish oral self-administration of and reinforcement from drugs using other species and substances (9, 10, 23, 24, 31) were effective in establishing orally delivered cocaine as a positive reinforcer of lever press responding in male C57BL/6J mice. Drinking of cocaine solutions containing gradually decreasing amounts of ethanol were utilized to expose the animals to the interoceptive effects of cocaine. Under these conditions, responding did not decrease, and in fact increased, as the concentration of ethanol was decreased to 0% and the concentration of cocaine was increased to 0.2 mg/ml. As a consequence, over the course of training, the amount of ethanol consumed per session decreased while the amount of cocaine consumed increased to a final average value in excess of 6 mg/kg. However, after training, when only a single lever press response was required to produce cocaine availability, responding remained high even for vehicle, and intake of the cocaine solution did not exceed intake of vehicle. This lack of extinction behavior is common at low FR sizes under conditions where behavior is contingent upon delivery of a strong reinforcer (16–18, 31).

When the number of lever presses required to produce cocaine availability was systematically increased, rates of drug-maintained lever pressing showed corresponding increases, but rates of responding for vehicle did not significantly increase. Further, at FR8, responding for delivery of cocaine significantly exceeded responding for vehicle. At FR8, when water alone was available, responding extinguished over a period of several sessions, but increased significantly when cocaine was reintroduced.

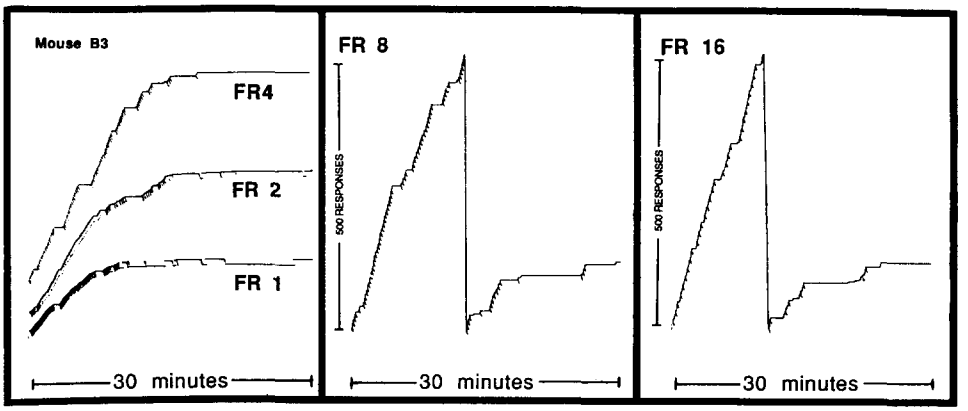

FIG. 3. Representive cumulative recordings of response patterns at 0.2 mg/ml cocaine for mouse B3 at FR's 1, 2, 4, 8 and 16. Completion of the first component in the chain schedule of reinforcement, lever presses, results in a vertical deflection of the pen. The pen returns to its point of deflection upon completion of the second component, 10 licks.

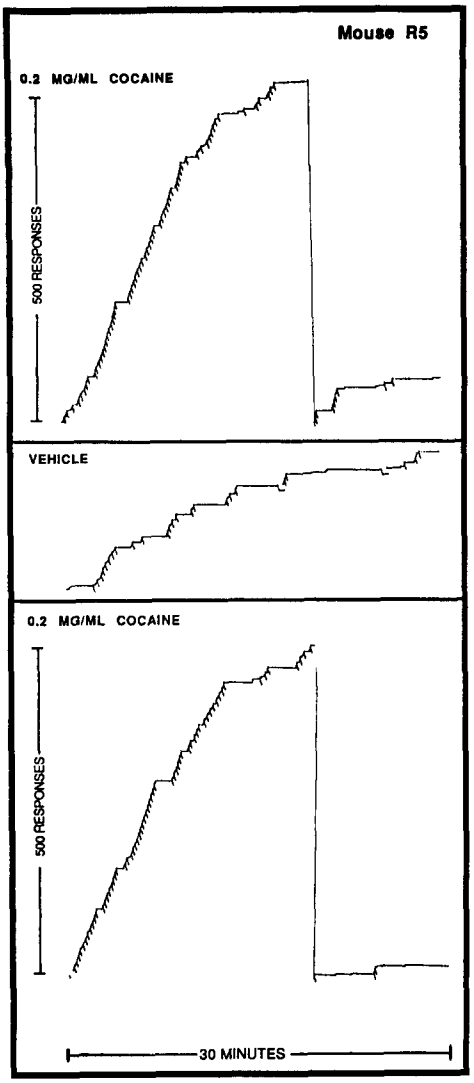

FIG. 4. Cumulative records of mouse R53 at FR8, 0.2 mg/ml cocaine and vehicle (water). Completion of the first component in the chain schedule of reinforcement, lever presses, results in a vertical deflection of the pen. The pen returns to its point of deflection upon completion of the second component, 10 licks.

Cocaine responding and drinking occurred at the highest rates during the initial portions of the 30-min sessions, with fewer responses occurring as the time within session progressed. This pattern of responding is consistent with patterns of responding which have been previously reported under similar FR schedules of IV cocaine injection in squirrel monkeys (16). In addition, this pattern of responding rules out a random activity explanation of lever pressing under cocaine conditions. The equipment and methods used in this study also rule out the possibility that continued lever press responding occurred in the absence of actual drug intake. In the present system, continued lever pressing has no effect without completion of the licking component of the operant chain. Thus the animal must complete the licking requirement and obtain drug delivery in order to reinitiate the lever pressing portion of the chain. Thus with this system, cumulative records of lever pressing are an accurate representation of actual drug delivery and intake. These results demonstrate that orally delivered cocaine can serve as a positive reinforcer, and thus extend to the oral route the range of conditions over which cocaine functions as a reinforcer. These findings also increase the number of substances abused by humans that have also been shown to function as reinforcers for C57BL/6J mice.

A common assumption is that cocaine is self-administered because of its behavioral stimulant effects. In the present experiments, however, mice consistently self-administered amounts of cocaine which appear to be below the threshold for increasing locomotor activity, and which instead may be associated with decreases in activity (11). Indeed, the decreases in rate of responding over time within sessions could be due to a cocaine-induced depressant effect on activity. While further studies need to be conducted, the present data suggest that while drugs of abuse may at certain doses produce increases in behavioral activity, those effects are not necessarily directly correlated with effects which maintain self-administration.

The results of the present experiments are important for several reasons. They systematically demonstrate that cocaine can function as a positive reinforcer when delivered orally—a route of cocaine administration desirable for chronic studies, especially in rodents, and a route associated with significant euphoric effects in humans. This is also the first demonstration, via any route of administration, of operant behavior reinforced by cocaine in mice, a mammalian species ideally suited for long-term genetic studies. An important point here is that in this study cocaine was established as a positive reinforcer in mice for which ethanol was previously established as a reinforcer. It will be important to determine the influence of prior drug-reinforced behavior on development of responding for cocaine, although initial results suggest that oral cocaine can indeed be established as a positive reinforcer in drug naive animals (12).

Self-administration procedures provide a valuable animal model of substance abuse. However, these experiments generally use a limited number of genetically undefined subjects, and experimental conditions are often varied independently across subjects. The building of a database using genetically defined populations is important in drug self-administration studies in order to elucidate the complex relationships among various drug-related behaviors and to precisely determine the behavioral principles, as well as the physiological and molecular substrates mediating these effects.

ACKNOWLEDGEMENTS

The authors thank Valerie Dyke for technical assistance and Dr. Gregory A. Lemaire for editorial comments. This research was supported in part by NIAAA New Investigator Research Award AA-06104/06924 (F.R.G.), by NIAAA Grant AA-07754 (F.R.G.), by NIDA Research Scientist Development Award DA-00944 (R.A.M.), and by the National Institute on Drug Abuse. Portions of this work were completed while F. R. George was Senior Fellow and R. A. Meisch was on sabbatical leave as Visiting Scientist at the NIDA Addiction Research Center.

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