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Effects of Chlordiazepoxide, Buspirone, and Serotonin Receptor Agonists and Antagonists on Responses of Squirrel Monkeys Maintained Under Second-Order Schedules of Intramuscular Cocaine Injection or Food Presentation

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ABSTRACT

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Lever pressing of squirrel monkeys was maintained under second-order schedules of either food presentation or cocaine injection. The first response after 3 min produced a 2 sec change in the color of a visual stimulus; the tenth stimulus presentation was followed by either an i.m. injection of cocaine (0.3, 1.0, or 2.0 mg/kg) or the delivery of food. The benzodiazepine chlordiazepoxide (0.3–5.6 mg/kg) increased responding maintained by food at doses that decreased cocaine-maintained responding. In contrast, buspirone, a novel nonbenzodiazepine anxiolytic (0.001–0.03 mg/kg), its analog gepirone (0.003–0.03 mg/kg), and the N serotonin 1A (5-HT_{1A}) agonist 8-hydroxy-2(di-*n*-propylamino)tetralin (8-OH-DPAT; 0.0003–0.001 mg/kg) increased cocaine-maintained responding at doses that decreased responding maintained by food. The inverse agonist at benzodiazepine receptors β-carboline-3-carboxylic acid ethyl ester (βCCE) only decreased response rates irrespective of the maintaining event. m-Chlorophenylpiperazine (mCPP), an agonist at 5-HT_{1B}

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receptors, increased responding maintained by food while only decreasing cocaine-maintained responding (0.001–0.03 mg/kg), whereas metergoline (0.1–0.3 mg/kg), a serotonin antagonist with affinity for both 5-HT_1 and 5-HT_2 receptors, produced large response rate increases in both groups of monkeys. Administration of the 5-HT_2 antagonist ketanserin (0.03–3.0 mg/kg), the 5-HT_{1A} compound spiroxatrine (0.0003–0.03 mg/kg), or the nonselective 5-HT agonist quipazine (0.003–1.0 mg/kg) resulted in dose-dependent response rate decreases in both groups. These results further differentiate buspirone and related compounds from typical anxiolytics and suggest a differential involvement of 5-HT_{1A} receptors in behaviors maintained by cocaine or food presentation.

Key words: novel anxiolytics, benzodiazepines, schedule controlled behavior, cocaine self-administration

INTRODUCTION

The behavioral effects of drugs depend on many variables such as ongoing rate of responding and schedule of reinforcement [Kelleher and Morse, 1968]. In addition, the type of event maintaining behavior can also result in differential drug effects, even when the rates and patterns of responding are similar [Barrett and Katz, 1981]. For example, chlordiazepoxide increases response rates of squirrel monkeys maintained by food under a fixed-interval schedule at doses that only decrease response rates maintained by the presentation of shock [Barrett, 1976]. Other drugs, such as *d*-amphetamine or chlorpromazine, have similar effects in both components, irrespective of the maintaining event [Barrett et al., 1981a,b; Katz, 1980; McKearney, 1974; Valentine et al., 1983].

In interpreting the effects of drugs on schedule-controlled behavior, it is sometimes important to assess the potential interactions between the pretreatment drug and recurring presentations of the maintaining event [cf. Katz, 1980; Valentine et al., 1983]. One method to eliminate recurring presentations of the reinforcer is to schedule its presentation only at the end of the session. Under second-order schedules, the presentation of a brief stimulus initially paired with a reinforcer can maintain responding over long periods of time in the absence of the primary reinforcer [Kelleher, 1966]. Responding under one schedule, termed the *unit schedule,* is treated as though it is a single response that is reinforced according to a second schedule. Completion of the unit schedule requirement results in a brief stimulus change that, upon completion of both second-order schedule requirements, produces the reinforcer. For example, under an FR 10 (FI 3 min:S) schedule, the first response after 3 min (FI) produces a brief stimulus changes, with the reinforcer following the 10th (FR) brief stimulus presentation. By scheduling the presentation of the primary reinforcer at the end of the session, changes in responding caused by repeated presentations of the consequent event can be avoided [Katz, 1980]. In addition, if the maintaining event is a drug, the extended sequences of behavior that typically occur under second-order schedules may be considered as analogous to the sequence of behaviors leading to drug self-administration in human drug abusers [Goldberg and Tang, 1977; Katz and Goldberg, 1990].

In squirrel monkeys lever pressing under second-order schedules, chlordiazepoxide has been shown to increase responding maintained by food at doses that decrease responding maintained by shock presentation [Barrett et al., 1981b]. However, chlordiazepoxide's effects on performances maintained under second-order schedules of cocaine injection, at present, are somewhat equivocal [Valentine et al., 1983]. One objective of the present study was to examine further the effects of chlordiazepoxide on responding maintained under this schedule.

The azaspirodecanedione buspirone, a novel nonbenzodiazepine anxiolytic, has generated much research comparing its effects to those of the benzodiazepines. In squirrel monkeys, buspirone's behavioral profile is quite different from that of chlordiazepoxide [Barrett and Witkin, 1990]. The behavioral effects of the benzodiazepines seem to be mediated through the

benzodiazepine–GABA receptor complex [Bosmann et al., 1977; Braestrup and Squires, 1977; Mohler and Okada, 1977; Tallman et al., 1980], while buspirone's behavioral actions, although initially believed to be dopaminergic [Taylor et al., 1982], appear to be mediated through the serotonin (5-HT) neurotransmitter system [Glaser and Traber, 1983; Vander Maelen and Wilderman, 1984] primarily through the 5-HT_{1A} receptor subtype [Peroutka, 1985].

In addition to a further evaluation of chlordiazepoxide's effects on responding maintained by cocaine injections, the present study also examined the behavioral effects of buspirone, the buspirone analog gepirone, and the inverse agonist β-carboline-3-carboxylic acid ethyl ester (βCCE) on performance of squirrel monkeys maintained under second-order schedules of either food presentation or cocaine injection. In addition, the behavioral activity of a number of serotonin agonists and antagonists was studied under the second-order schedules. The serotonin compounds studied were metergoline, a serotonin antagonist with equal binding affinity for the 5-HT_1 and 5-HT_2 receptor; the 5-HT_2 receptor antagonist ketanserin; spiroxatrine, a suggested 5-HT_{1A} antagonist [Nelson and Taylor, 1986]; quipazine, an agonist at 5-HT_1 and 5-HT_2 receptors; the 5-HT_{1A} ligand 8-hydroxy-2(di-*n*-propylamino)tetralin (8-OH-DPAT); and the 5-HT_{1B} agonist m-chlorophenylpiperazine (mCPP).

MATERIALS AND METHODS

Subjects

Seven male squirrel monkeys *(Saimiri sciurea),* maintained at approximately 85% of their free-feeding body weights, served as subjects. At the start of the experiment, body weights ranged from 700 to 825 g. All subjects were individually housed and had unlimited access to water in the colony room. Once daily, at least 1 hr after experimental sessions, they were fed a sufficient amount of Purina Monkey Chow to maintain their body weights. Four monkeys (MS-126, MS-128, MS-130, and MS-131) were experimentally naive, while MS-4, MS-113, and MS-114 had experience under other schedules of reinforcement but had not received drugs for at least 3 months prior to the start of the study. No subject had previously received drug injections contingent upon their behavior.

Apparatus

During experimental sessions, subjects were seated in a Plexiglas chair [Hake and Azrin, 1963]. Each chair was equipped with a response lever (BRS/LVE, No. 121-05, Beltsville, MD) mounted approximately 8 cm above the waist plate, three pairs of 7.5 W stimulus lights located at eye level behind the front panel, and a food pellet dispenser (R. Gerbrands, No. G5100, Arlington, MA). A downward force of 20 g (0.196 N) or greater was required to be recorded as a response. Each response produced a click of a relay mounted behind the front panel of the chair. During testing, chairs were enclosed within a ventilated, sound-attenuated chamber, with white masking noise continuously present.

Procedure

All subjects were initially trained under a 3 min fixed-interval (FI) schedule. The first response after 3 min produced a 2 sec stimulus change, from white to yellow, followed by the delivery of a 300 mg banana-flavored food pellet. During successive sessions, the first response after 3 min produced only the 2 sec stimulus change, with completion of successive intervals producing the brief stimulus and food. Each increase in fixed-ratio value was followed by an increase in the number of food pellets delivered. Under the final schedule parameters, completion of each 3 min FI unit produced the brief stimulus, with the first response after the 10th fixed-interval producing a 3 min stimulus change and the delivery of 10 food pellets.

With three monkeys, responding was maintained by cocaine injections, while in four

subjects food was used to maintain responding. Following completion of all dose-response curves under the food schedule, one monkey (MS-126) was trained under the schedule with cocaine and selected dose-response curves were redetermined (see below).

Cocaine-Maintained Performance

When food-maintained responding under the second-order schedule was considered stable by visual inspection of daily cumulative records, MS-128, MS-130, and MS-131 were administered 0.3 mg/kg cocaine during the final stimulus change, along with 10 food pellets. Following food delivery, the chamber door was opened and cocaine was injected into the calf muscle. This injection procedure lasted no longer than 10 sec. Subsequently, in the next several sessions the number of food pellets was gradually reduced to zero, while the cocaine dose was increased to 1.0 mg/kg (MS-128, MS-130) or to 2.0 mg/kg (MS-126) or remained at 0.3 mg/kg (MS-131). Cocaine was administered 0.5 ml/kg body weight. To control for drug exposure, subjects whose lever pressing was maintained by food presentation received 1.0 mg/kg cocaine in the colony room at least 1 hr after the session.

Drug Testing

Experimental sessions were conducted 5 days a week, with drugs other than cocaine usually administered on Tuesdays and Fridays. Thursdays and sessions preceded by saline injections served as control sessions. Drugs under investigation in the present study were chlordiazepoxide HCl (Hoffman-La Roche Inc., Nutley, NJ), buspirone HCl and gepirone HCl (Bristol-Myers Co., Evansville, IN), β-carboline-3-carboxylic acid ethyl ester HCl (βCCE; synthesized by J. Cook and T. Hagen, University of Wisconsin, Milwaukee, WI), metergoline (Farmitalia, Milan, Italy), ketanserin tartrate and spiroxatrine HCl (Jannsen Pharmaceutica, Beerse, Belgium), (±)-8-hydroxy-2(di-*n*-propylamino)tetralin HBr (8-OH-DPAT), and m-chlorophenypiperazine HCl (mCPP; Research Biochemicals Inc., Natick, MA). Drugs were prepared immediately before the session and were given intramuscularly (i.m.) into the calf muscle in a volume of 1.0 ml/kg body weight. All compounds were dissolved in saline except metergoline and ketanserin, which were dissolved in sterile water. In addition, metergoline required one to two drops of 8.5% lactic acid to facilitate solubility. All drugs were administered immediately before the session except chlordiazepoxide, which was administered 60 min prior to testing. Subjects received all doses in random order, with most points determined at least twice. Doses are expressed as the salt forms except for metergoline, which is expressed as the free base.

Data Analysis

Data were collected on digital counters and elapsed time meters. Response rates were calculated by dividing total responses by session time (seconds). Dose-response curves are expressed as percentage of Thursday control sessions. Data are presented for each individual subject and as group averages. Drug effects for each subject were considered significant if the average rate of responding following presession drug administration ± 1 S.E. did not overlap the average control rate ± 1 S.E.

RESULTS

Responding was reliably maintained by both food or cocaine injections, with positively accelerated response rates across the session. Control responding of two subjects is shown in the top panel of Figure 1. Short pauses occurred after brief stimulus presentations, followed by increases in responding until the next stimulus presentation; in some monkeys whose responding was maintained by food, these pauses and within-stimulus accelerations were much more pronounced. Monkeys whose responding was maintained by food had slightly higher rates compared with cocaine-maintained monkeys (Table 1). Response rates remained relatively

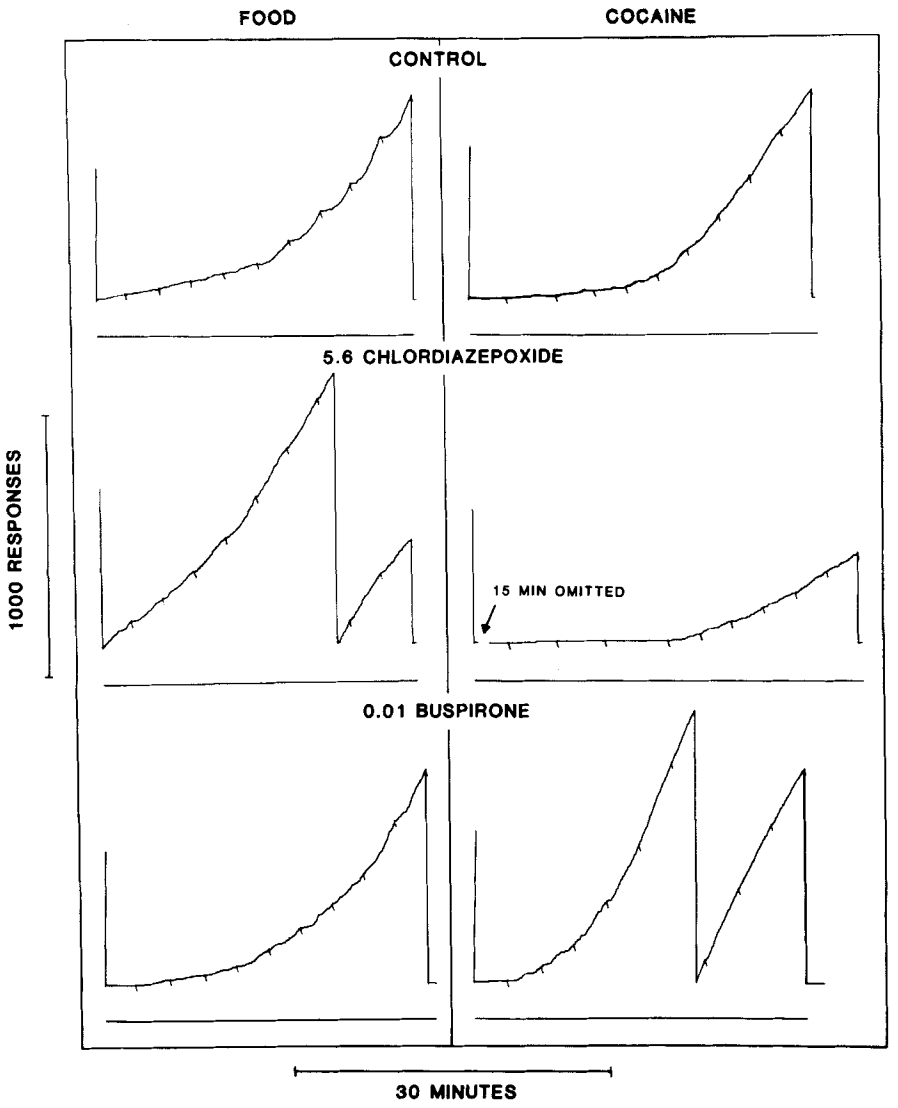

Fig. 1. Control performances and effects of chlordiazepoxide (5.6 mg/kg) and buspirone (0.01 mg/kg) in two monkeys whose responding was maintained by either food presentation (ms = 126) or cocaine injection (ms = 130). The stepper increased with each response, and a downward deflection of the pen denotes a 2 sec stimulus change.

stable for all subjects except MS-131, whose cocaine-maintained response rates gradually increased throughout the study.

Prior to dose-response curve determinations, saline was substituted for cocaine to verify that cocaine was maintaining responding. In all subjects, response rates decreased to near zero within three to five sessions. To reinstate responding, cocaine was readministered, initially under an FI 3 min schedule. Between 15 and 30 sessions were required before all subjects' responding under the second-order schedule was again maintained by cocaine.

Chlordiazepoxide (0.3–5.6 mg/kg) increased food-maintained response rates at doses that only decreased responding maintained by cocaine (Fig. 2). These rate increases were

TABLE 1. Control rates of responding (r/s) for each subject*

Food	Cocaine
MS-126, 0.37 (0.02)	MS-128, 0.04 (0.002)
MS-113, 0.12 (0.006)	MS-130, 0.38 (0.02)
MS-114, 0.43 (0.04)	MS-131, 0.17 (0.04)
MS-4, 0.98 (0.10)	MS-126, 0.38 (0.05)

*Numbers represent the average of all control sessions throughout the study. Figures in parentheses indicate 1 S.E.

significant in all three monkeys tested, while no monkey whose responding was maintained by cocaine showed increases in response rates following chlordiazepoxide. The middle panel in Figure 1 shows representative cumulative records for two subjects following 5.6 mg/kg chlordiazepoxide. Responding maintained by cocaine injections was greatly disrupted and was characterized by an initially long pause, followed by an overall decrease in the number of responses, while responding maintained by food presentations was characterized by decreases in the initial pause at the beginning of the session and overall rate increases throughout the entire session.

Buspirone (0.001–0.03 mg/kg) significantly increased responding maintained by cocaine in two subjects, while the third subject showed rate increases of approximately 120% of control, which fell just short of significance (Fig. 2). One monkey showed rate increases in food-maintained responding following buspirone, while all other subjects whose responding was maintained by food showed dose-dependent decreases (Fig. 2). Buspirone's rate decreasing effects were at least 10 times as potent as chlordiazepoxides. Cumulative records from two sessions preceded by 0.01 mg/kg buspirone are shown in the lower panel of Figure 1. Following buspirone, cocaine-maintained responding was characterized by decreased pause time and increased overall response rates from the first interval to the end of the session (Fig. 1). These effects were larger than the food-maintained rate increases seen following chlordiazepoxide.

Similar selectivity of drug effect was reported for gepirone (0.003–0.03 mg/kg). Responding maintained by cocaine was increased at doses that had no effect or decreased response rates of food-maintained monkeys (Fig. 2). Although responding was significantly increased following gepirone in two of three cocaine-maintained subjects, these increases were much smaller compared with buspirone (peak effects were 125% vs. 200% of control for gepirone and buspirone, respectively).

The inverse agonist βCCE (0.003–0.03 mg/kg) only decreased response rates in all subjects irrespective of the maintaining event. These rate-decreasing effects were observed at doses at least 100 times lower than those that produced comparable effects with chlordiazepoxide (Fig. 2).

Figure 3 shows dose-response curves determined for three serotonin antagonists. Metergoline significantly increased response rates in all cocaine-maintained subjects and in two of three monkeys whose responding was maintained by food. The largest rate-increasing effects were observed between 0.10 and 0.30 mg/kg. Administration of ketanserin (0.03–3.0 mg/kg) or spiroxatrine (0.0003–0.03 mg/kg) only decreased response rates in a dose-dependent manner, irrespective of the maintaining event. Spiroxatrine was approximately 100 times more potent than metergoline or ketanserin in decreasing response rates (Fig. 3).

Dose-effect curves for the serotonin agonists quipazine, mCPP, and 8-OH-DPAT are shown in Figure 4. Quipazine (0.003–1.0 mg/kg) decreased response rates by all subjects in both groups. mCPP, a 5-HT_{1B} agonist, significantly increased food-maintained responding in two of three subjects at doses that only decreased responding maintained by cocaine (Fig. 4). However, monkeys differed considerably in the doses at which this compound increased responding so that the average curve, shown at the right, does not reflect the increases that

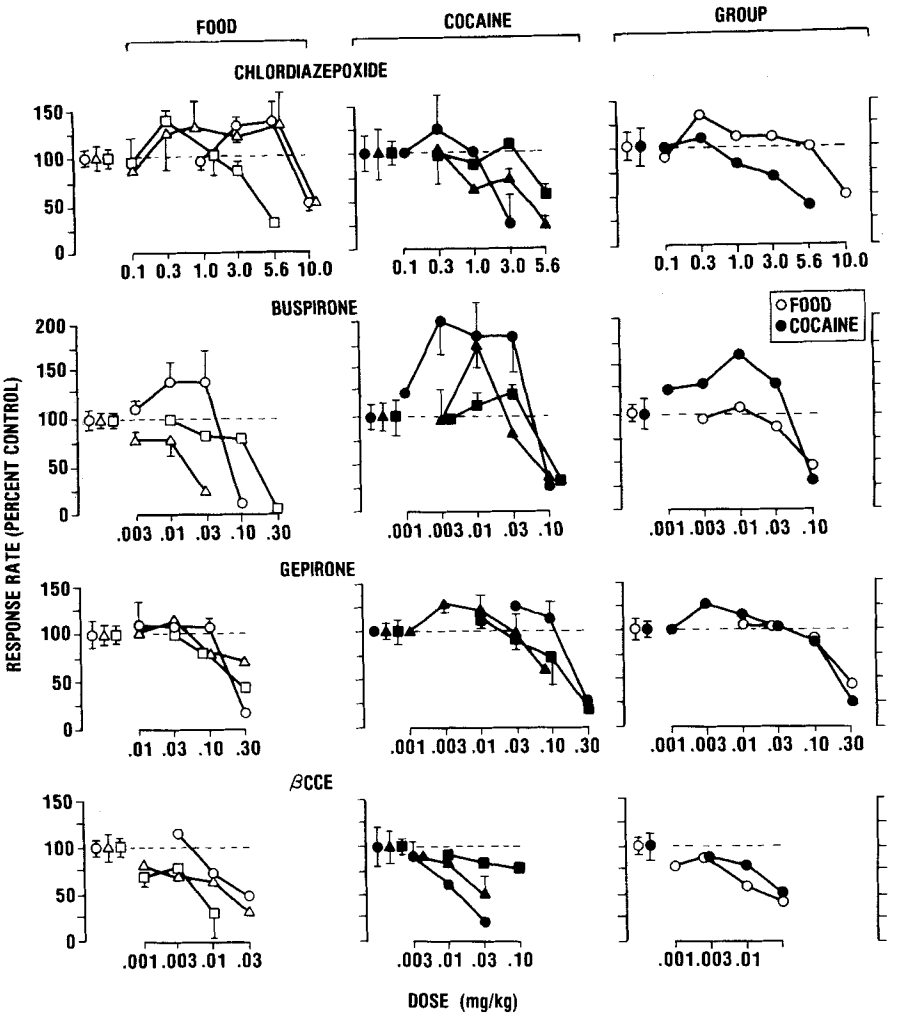

Fig. 2. Effects of chlordiazepoxide, buspirone, gepirone, and βCCE on second-order responding maintained by either food presentation (open symbols; left panel) or cocaine injection (filled symbols; middle panel) for each subject and as group averages (right). Response rate is presented as a percentage of the overall rate of responding from control sessions. The dotted horizontal lines represent 100% of control responding; vertical lines denote 1 S.E. of response rates. Subjects are represented as follows: ○, MS-126; △, MS-113; □, MS-4 (chlordiazepoxide) and MS-114 (buspirone, gepirone, βCCE); ●, MS-128; ▲, MS-130 (chlordiazepoxide, buspirone, gepirone) and MS-126 (βCCE); ■, MS-131.

occurred in two of three monkeys. The 5-HT_{1A} ligand 8-OH-DPAT (0.0003–0.003 mg/kg) increased response rates in two of three monkeys whose responding was maintained by cocaine at doses that only decreased food-maintained responding (Fig. 4). Again, the group curve, consisting of the average of three monkeys, does not reflect these changes with 8-OH-DPAT in individual subjects.

DISCUSSION

Under the second-order schedule used in the present study, food presentations maintained responding at slightly higher rates compared with cocaine injections, although the

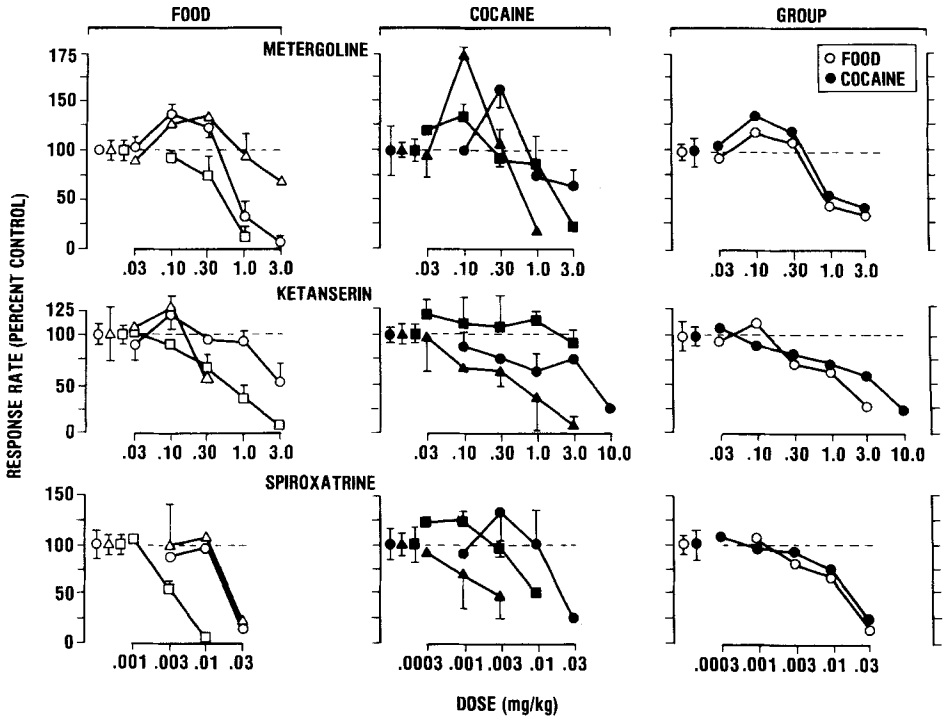

Fig. 3. Effects of three serotonin antagonists (metergoline, ketanserin, and spiroxatrine) on second-order responding maintained by either food presentation (left) or cocaine injection (middle) for each subject and as group averages (right). Details are as described in Figure 2. Subjects are represented as follows: ○, MS-126; △, MS-113; □, MS-4 (metergoline, ketanserin) and MS-114 (spiroxatrine); ●, MS-128; ▲, MS-130; ■, MS-131 (metergoline, ketanserin) and MS-126 (spiroxatrine).

positively accelerated pattern of responding was generally comparable in all subjects. Systematic manipulations of the cocaine dose were not made in this study, although it has been shown to be an important factor in controlling the rate of responding under second-order schedules [Katz, 1980]. However, it is clear that cocaine was serving as a reinforcer because saline substitution resulted in response rate decreases to near 0 r/s within five sessions.

Presession administration of chlordiazepoxide consistently increased responding maintained by food at doses that only decreased cocaine-maintained responding. Earlier attempts to document chlordiazepoxide's effects on cocaine-maintained performance under a second-order schedule had produced equivocal results in that some monkeys showed increases in responding, whereas others did not [Valentine et al., 1983]. In the present study, chlordiazepoxide's effects occurred at widely different control rates, suggesting that the rate increases were not directly related to ongoing response rate. Since all subjects whose responding was maintained by food presentation also received cocaine daily, chlordiazepoxide's selectivity of action is most likely the result of differences in maintaining events and not a result of differential drug exposure. These rate increases in food-maintained responding following chlordiazepoxide replicate an earlier finding using second-order schedules by Barrett et al. [1981b]. Interestingly, chlordiazepoxide's rate-decreasing effects on cocaine-maintained responding appear similar to the effects reported in monkeys responding under a second-order schedule of shock presentation [Barrett et al., 1981b].

βCCE decreased response rates in both groups of subjects, irrespective of the maintain-

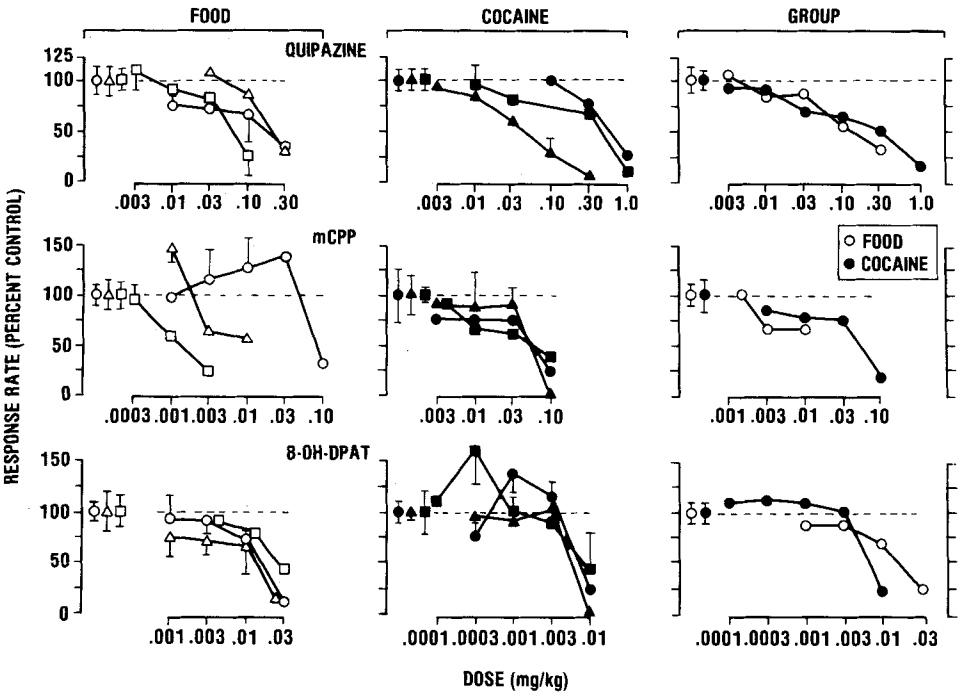

Fig. 4. Effects of three serotonin agonists (quipazine, mCPP, 8-OH-DPAT) on second-order responding maintained by either food presentation (left) or cocaine injection (middle) for each subject and as group averages (right). Details are as described in Figure 2. Subjects are represented as follows: ○, MS-126; △, MS-113; □, MS-4 (quipazine) and MS-114 (mCPP, 8-OH-DPAT); ●, MS-128; ▲, MS-130; ■, MS-131 (quipazone, 8-OH-DPAT) and MS-126 (mCPP).

ing event. Inverse agonists, such as the β-carboline derivatives, have been shown to produce effects opposite those of benzodiazepine agonists [Corda et al., 1983; Ninan et al., 1982]. For example, βCCE increases shock-maintained responding at doses that decrease responding maintained by food, while chlordiazepoxide increases food-maintained responding and decreases responding maintained by shock [Barrett et al., 1986]. The inverse agonists have been described as anxiogenic because of their behavioral, physiological, and pharmacological actions [Ninan et al., 1982]. Comparable decreases in both food- and cocaine-maintained responding in the present study suggest that, with the above exception in which increases in responding maintained by response-produced shock were observed, these compounds typically decrease most conditioned behaviors. It would be interesting to examine the effects of the inverse agonists in animals undergoing withdrawal from chronic cocaine or other drugs in so far as drug withdrawal has been suggested to produce a constellation of behaviors characterized as anxiety.

The behavioral profile of buspirone is quite different from that of the benzodiazepines [Barrett and Witkin, 1990]. For example, buspirone does not increase or only slightly increases punished responding by squirrel monkeys in contrast to the large increases observed following benzodiazepine administration [Sepinwall, 1985; Weissman et al., 1984]. The present results confirm and extend the observation that buspirone's behavioral effects are different from those of the benzodiazepines. Buspirone decreased food-maintained responding while increasing responding maintained by cocaine injections. *d*-Amphetamine has also been shown to increase cocaine-maintained responding under second-order schedules [Katz, 1980]

and will itself maintain responding in many species. Buspirone does not maintain responding when substituted for intravenous cocaine [Balster and Woolverton, 1982]. However, while *d*-amphetamine increases cocaine-maintained responding, its effects under second-order schedules are very nonselective (i.e., it also increases food-maintained performance). Selectivity of drug action in animals responding under second-order schedules has always been reported as increases in food- and decreases in cocaine- or shock-maintained responding, while nonselective actions have included increases in food- and cocaine-maintained performance (e.g., *d*-amphetamine) or decreases in both (e.g., promazine) [Katz, 1980]. Thus the effects of buspirone differ from those of most drugs studied under these conditions.

Because cocaine injections were limited to the end of the session, buspirone's rate-increasing effects were not due to blockade of cocaine's rate-altering actions. Goldberg et al. [1976] found that pretreatment administration of the opiate antagonist nalorphine increased response rates maintained under a second-order schedule of morphine injections in rhesus monkeys. These increases in response rates following nalorphine administration are similar to the effects reported under schedules in which response-contingent morphine injections are available throughout the session [Goldberg et al., 1971]. No data are available on whether buspirone or other serotonin compounds antagonize the reinforcing stimulus actions of cocaine under schedules of repeated cocaine administration.

In the present study, the effects of buspirone and the buspirone analog gepirone on second-order responding were qualitatively similar, although the increases in cocaine-maintained responding were much larger following buspirone administration. In vitro binding and in vivo behavioral studies have shown that, in addition to its dopaminergic properties [McMillen et al., 1983; Riblet et al., 1982; Taylor et al., 1982; Wood et al., 1983], buspirone has a substantial serotonergic component, primarily acting through the 5-HT_{1A} receptor subtype [Mansbach et al., 1988; Peroutka, 1985]. Gepirone has a similar serotonin component, but lacks the dopamine antagonist actions of buspirone [McMillen and Mattiace, 1983]. Similar behavioral effects of buspirone and gepirone therefore suggest serotonergic involvement. In the present study, the 5-HT_{1A} ligand 8-OH-DPAT also produced effects that were similar to those of buspirone and gepirone, thereby confirming a common mechanism of action for these three drugs. Thus it appears that drugs acting at the 5-HT_{1A} receptor can produce unique effects on cocaine-maintained responding that suggest other avenues for exploring the potent reinforcing effects of these psychomotor stimulants.

The specificity of action within the serotonin system is apparent when the effects of mCPP are compared with those of other serotonin agonists. mCPP, AN agonist that binds to the 5- HT_{1B} receptor, produced modest increases in food-maintained responding. These effects, although not large, were in the opposite direction from those of buspirone, gepirone, and 8-OH-DPAT. Although no 5-HT_{1B} receptors have yet been identified in primates [Hoyer et al., 1986], these data may indicate that this receptor subtype does exist in primates, although the numbers may be small.

Under the second-order schedules used in the present study metergoline increased response rates in squirrel monkeys irrespective of the maintaining event. Metergoline, which binds with equal affinity to the 5-HT_1 and 5-HT_2 receptors, has been shown to increase responding by squirrel monkeys under food- or shock-presentation schedules and to increase responding that has been suppressed by punishment [Brady and Barrett, 1985a,b]. Ketanserin, which has high affinity for the 5-HT_2 receptor, only decreased responding under the second-order schedule, suggesting that the rate increases reported following metergoline administration were mediated through the 5-HT_1 receptor. It is at present not clear why blockade of the 5-HT_1 receptor produced effects similar to agonist actions at the 5-HT_{1A} receptor. It may be that buspirone, gepirone, and 8-OH-DPAT are acting presynaptically at the 5-HT_1 autoreceptor [Goodwin et al., 1985; Gozlan et al., 1983], while metergoline is acting postsynaptically.

The reported 5-HT_{1A} antagonist spiroxatrine [Nelson and Taylor, 1986] only decreased response rates in squirrel monkeys irrespective of the maintaining event. Recent evidence

suggests that spiroxatrine may in fact be a 5-HT_{1A} agonist rather than an antagonist [Barrett et al., 1989]. However, the behavioral profile of spiroxatrine in the present study is not similar to those of the other 5-HT_{1A} agonists buspirone, gepirone, and 8-OH-DPAT. Spiroxatrine, like buspirone, has a large dopaminergic component and was initially introduced as an antipsychotic [Niemegeers et al., 1964]. In pigeon CSF, spiroxatrine and buspirone decrease levels of 5-hydroxyindoleacetic acid (5-HIAA), the primary metabolite of 5-HT, and increase the levels of the dopamine metabolite homovanillic acid (HVA). However, the levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) were only slightly increased following buspirone, while being significantly increased after spiroxatrine administration [Barrett et al., 1989]. The significance of the noradrenergic involvement has yet to be determined but may be responsible for the different effects of buspirone and spiroxatrine on cocaine-maintained responding.

In summary, the effects of chlordiazepoxide, buspirone, and the 5-HT_{1A} agonists 8-OH-DPAT and gepirone depended on the maintaining event. Chlordiazepoxide increased food- and decreased cocaine-maintained responding, whereas the 5-HT_{1A} agonists produced the opposite effects. The present results provide further evidence for the atypical actions of buspirone compared with chlordiazepoxide and support data suggesting that buspirone's actions are mediated through the serotonin system. Although most studies examining the effects of pretreatment drug administration on cocaine-maintained performance have used dopamine compounds, results from the present study suggest that serotonin neurotransmission may also mediate some behaviors maintained by cocaine.

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REFERENCES

Balster, R.L. and Woolverton, W.L.: Intravenous buspirone self-administration in rhesus monkeys. J. Clin. Psychiatry **43:**34–37, 1982.

Barrett, J.E.: Effects of alcohol, chlordiazepoxide, cocaine, and pentobarbital on responding maintained under fixed-interval schedules of food or shock presentation. J. Pharmacol. Exp. Ther. **196:** 605–615, 1976.

Barrett, J.E., Brady, L.S., Stanley, J.A., Mansbach, R.S., and Witkin, J.M.: Behavioral studies with anxiolytic drugs. II. Interactions of zopiclone with ethyl-*B*-carboline-3-carboxylate and Ro 15-1788 in squirrel monkeys. J. Pharmacol. Exp. Ther. **236:**313–319, 1986.

Barrett, J.E. and Katz, J.L.: Drug effects on behaviors maintained by different events. In Thompson T., Dews, P.B., and McKim, W.A. (eds.): "Advances in Behavioral Pharmacology." New York: Academic Press, 1981, Vol. 3, pp. 119–168.

Barrett, J.E., Katz, J.L., and Glowa, J.R.: Effects of *d*-amphetamine on responding under second-order schedules of food presentation, electric shock presentation or stimulus-shock termination. J. Pharmacol. Exp. Ther. **218:**692–700, 1981a.

Barrett, J.E., Olmstead, S.N., Lei, Z., Harrod, C., Hoffmann, S.M., Glover, K., Nader, M.A., and Weissman, B.A.: Behavioral neurochemical and discriminative stimulus effects of spiroxatrine, a putative 5-HT_{1A} receptor antagonist. In Archer, T., Bevan, P., Broekkamp, R., Cools, L., and Olivier, B. (eds.): "Behavioral Pharmacology of 5-HT." Hillsdale, NJ: Lawrence Erlbaum Associates, 1989, pp. 449–452.

Barrett, J.E., Valentine, J.O., and Katz, J.L.: Effects of chlordiazepoxide and *d*-amphetamine on responding of squirrel monkeys maintained under concurrent or second-order schedules of response-produced food or electric shock. J. Pharmacol. Exp. Ther. **219:**199–206, 1981b.

Barrett, J.E. and Witkin, J.M.: Buspirone in animal models of anxiety. In Tunnicliff, G., Eison, A.S., and Taylor, D.P. (eds.): "Buspirone: Mechanisms and Clinical Aspects." New York: Academic Press (in press), 1990.

Bosmann, H.B., Case, K.R., and Distefano, P.: Diazepam receptor characterization: Specific binding of a benzodiazepine to macromolecules in various areas of rat brain. FEBS Lett. **82:**368, 1977.

Brady, L.S. and Barrett, J.E.: Effects of serotonin receptor antagonists on punished responding maintained by stimulus-shock termination or food presentation in squirrel monkeys. J. Pharmacol. Exp. Ther. **234:**106–112, 1985a.

Brady, L.S. and Barrett, J.E.: Effects of serotonin receptor agonists and antagonists on schedule-controlled behavior of squirrel monkeys. J. Pharmacol. Exp. Ther. **235:**436–441, 1985b.

Braestrup, C. and Squires, R.F.: Specific benzodiazepine receptors in rat brain characterized by high affinity [^{3}H]diazepam binding. Proc. Natl. Acad. Sci. USA **74:**3805–3809, 1977.

Corda, M.G., Blaker, W.D., Mendelson, W.B., Guidotti, A., and Costa, E.: *B*-carbolines enhance shock-induced suppression of drinking in rats. Proc. Natl. Acad. Sci. USA **80:**2072, 1983.

Glaser, T. and Traber, J.: Buspirone: Action on serotonin receptors in calf hippocampus. Eur. J. Pharmacol. **88:**137–138, 1983.

Goldberg, S.R., Morse, W.H., and Goldberg, D.M.: Behavior maintained under a second-order schedule by intramuscular injection of morphine or cocaine in rhesus monkeys. J. Pharmacol. Exp. Ther. **199:**278–286, 1976.

Goldberg, S.R. and Tang, A.H.: Reinforcement of behavior by morphine injections. In Blum, K. (ed.): "Alcohol and Opiates." New York: Academic Press, 1977, pp. 341–357.

Goldberg, S.R., Woods, J.H., and Schuster, C.R.: Nalorphine-induced changes in morphine self-administration in rhesus monkeys. J. Pharmacol. Exp. Ther. **176:**464–471, 1971.

Goodwin, G.M., De Souza, R.J., and Green, A.R.: The pharmacology of the hypothermic response in mice to 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT): A model of presynaptic 5-HT_1 function. Neuropharmacology **24:**1187–1194, 1985.

Gozlan, H., El Mestikaway, S., Pichat, L., Glowinski, J., and Hamon, M.: Identification of presynaptic serotonin autoreceptors using a new ligand: ^{3}H-PAT. Nature **305:**140–142, 1983.

Hake, D.F. and Azrin, N.H.: An apparatus for delivering pain shock to monkeys. J. Exp. Anal. Behav. **6:**297–298, 1963.

Hoyer, D., Pazos, A., Probst, A., and Palacious, J.M.: Serotonin receptors in human brain. I. Characterization and autoradiographic localization of 5-HT_{1A} recognition sites: Apparent absence of 5-HT_{1B} recognition sites. Brain Res. **376:**85–96, 1986.

Katz, J.L.: Second-order schedules of intramuscular cocaine injection in the squirrel monkey: Comparisons with food presentation and effects of *d*-amphetamine and promazine. J. Pharmacol. Exp. Ther. **212:**405–411, 1980.

Katz, J.L. and Goldberg, S.R.: Second-oreder schedules of drug injection: Implications for understanding reinforcing effects of abused drugs. In Mello, N.K. (ed.): "Advances in Substance Abuse." Greenwich, CT: JAI Press, Inc., 1990, Vol. 3 (in press).

Kelleher, R.T.: Conditioned reinforcement in second-order schedules. J. Exp. Anal. Behav. **9:**475–485, 1966.

Kelleher, R.T. and Morse, W.H.: Determinants of the specificity of behavioral effects of drugs. Ergeb. Physiol. Biol. Chem. Exp. Pharmakol. **60:**1–56, 1968.

Mansbach, R.S., Harrod, C., Hoffmann, S.M., Nader, M.A., Lei, Z., Witkin, J.M., and Barrett, J.E.: Behavioral studies with anxiolytic drugs. V. Behavioral and in vivo neurochemical analyses in pigeons of drugs that increase punished responding. J. Pharmacol. Exp. Ther. **246:**114–120, 1988.

McKearney, J.W.: Effects of *d*-amphetamine, morphine and chlorpromazine on responding under fixed-interval schedules of food presentation or electric shock presentation. J. Pharmacol. Exp. Ther. **190:**141–153, 1974.

McMillen, B.A., Matthews, R.T., Sanghera, M.K., Shepard, P.D., and German, D.C.: Dopamine receptor antagonism by the novel antianxiety drug, buspirone. J. Neurosci. **3:**733–738, 1983.

McMillen, B.A. and Mattiace, L.A.: Comparative neuropharmacology of buspirone and MJ-13805, a potential anti-anxiety drug. J. Neural Transm. **57:**255–265, 1983.

Mohler, H. and Okada, T.: Benzodiazepine receptor: Demonstration in the central nervous system. Science **198:**849–851, 1977.

Nelson, D.L. and Taylor, D.P.: Spiroxatrine: A selective serotonin 1A receptor antagonist. Eur. J. Pharmacol. **124:**207–208, 1986.

Niemegeers, C.J.E., Verbruggen, F.J., Van Neuten, J.M., and Janssen, P.A.J.: Spiroxamide (R 5188):

A new compound producing morphine-like and chlorpromazine-like effects in animals. Int. J. Neuropharmacol. **2:**349–354, 1964.

Ninan, P.T., Insel, T.M., Cohen, R.M., Cook, J.M., Skolnick, P., and Paul, S.M.: Benzodiazepine receptor-mediated experimental "anxiety" in primates. Science **218:**1332–1334, 1982.

Peroutka, S.J.: Selective interaction of novel anxiolytics with 5-hydroxytryptamine 1A receptors. Biol. Psychiatry **20:**971–979, 1985.

Riblet, L.A., Taylor, D.P., Eison, M.S., and Stanton, H.C.: Pharmacology and neurochemistry of buspirone. J. Clin. Psychiatry **43:**11–16, 1982.

Sepinwall, J.: Behavioral effects of antianxiety agents: Possible mechanisms of action. In Seiden, L.S. and Balster, R.L. (eds.): "Behavioral Pharmacology: The Current Status." New York: Alan R. Liss, Inc., 1985, pp. 181–203.

Tallman, J.F., Paul, S.M., Skolnick, P., and Gallagher, D.W.: Receptors for the age of anxiety: Pharmacology of the benzodiazepines. Science **207:**274–281, 1980.

Taylor, D.P., Riblet, L.A., Stanton, H.C., Eison, A.S., Eison, M.S., and Temple, D.L. Jr.: Dopamine and antianxiety activity. Pharmacol. Biochem. Behav. **17 (Suppl. 1):**25–35, 1982.

Valentine, J.O., Katz, J.L., Kandel, D.A., and Barrett, J.E.: Effects of cocaine, chlordiazepoxide, and chlorpromazine on responding of squirrel monkeys under second-order schedules of IM cocaine injection or food presentation. Psychopharmacology **81:**164–169, 1983.

Vander Maelen, C.P. and Wilderman, R.C.: Iontophoretic and systemic administration of the non-benzodiazepine anxiolytic drug buspirone causes inhibition of serotonergic dorsal raphe neurons in rats. Fed. Proc. **43:**947, 1984.

Weissman, B.A., Barrett, J.E., Brady, L.S., Witkin, J.M., Mendelson, W.B., Paul, S.M., and Skolnick, P.: Behavioral and neurochemical studies on the anticonflict actions of buspirone. Drug Dev. Res. **4:**83–93, 1984.

Wood, P.L., Nair, N.P.V., Lal, S., and Etienne, P.: Buspirone: A potent atypical neuroleptic. Life Sci. **33:**269–273, 1983.