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Distinctive Behavioral Effects of the Pyrazoloquinoline CGS 8216 in Squirrel Monkeys[1]

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WETTSTEIN, J. G. AND R. D. SPEALMAN. *Distinctive behavioral effects of the pyrazoloquinoline CGS 8216 in squirrel monkeys*. PHARMACOL BIOCHEM BEHAV 29(4) 741–745, 1988.—The behavioral effects of the pyrazoloquinoline CGS 8216 were studied in squirrel monkeys trained to respond under a fixed-interval (FI) schedule of food presentation. Dose-effect curves were determined by administering cumulative doses IV during timeout periods that preceded sequential components of the FI schedule. CGS 8216 (0.1–3.0 mg/kg) produced dose-related decreases in the rate of FI responding. In comparison, diazepam (0.1–3.0 mg/kg) had biphasic effects under identical conditions: intermediate doses increased the rate, whereas high doses decreased the rate of FI responding. Pretreatment with the benzodiazepine antagonist Ro 15-1788 (3.0 or 5.6 mg/kg) attenuated the decreases in response rate normally produced by high doses of CGS 8216. The behavioral effects of CGS 8216 were not altered systematically by pretreatment with either diazepam (0.3–3.0 mg/kg) or the α_2-adrenergic agonist clonidine (0.01–0.03 mg/kg). The results suggest that CGS 8216 has benzodiazepine inverse agonist effects on schedule-controlled behavior of squirrel monkeys. CGS 8216 can, however, be distinguished from inverse agonists of the β-carboline type on the basis of its effects in the presence of diazepam or clonidine.

CGS 8216 Pyrazoloquinoline Benzodiazepine Inverse agonist Ro 15-1788 Diazepam β-Carboline Schedule-controlled behavior Monkeys

LIGANDS for benzodiazepine recognition sites can be broadly classified as agonists, antagonists and inverse agonists based on their behavioral and neurophysiological actions. Both antagonists such as Ro 15-1788 and inverse agonists such as ethyl-β-carboline-3-carboxylate (β-CCE) block the effects of benzodiazepine agonists. Unlike benzodiazepine antagonists, however, inverse agonists also have intrinsic effects at low doses that are largely opposite to the effects of agonists. For example, β-CCE has been found to produce an anxiety-like syndrome in rhesus monkeys [14], to decrease rather than increase the rate of suppressed (punished) responding in squirrel monkeys [1,2], and to potentiate rather than block audiogenic seizures in rodents [10].

CGS 8216 (2-phenylpyrazolo[4,3-c]quinolin-3[5H]-one) is a potent ligand for benzodiazepine recognition sites [5] and can block the effects of benzodiazepine agonists in animals [11, 18, 24]. Although structurally unrelated to the β-carboline inverse agonists, CGS 8216 appears to have some intrinsic effects in common with β-CCE. For example, CGS 8216 has been found to decrease rather than increase water licking that is suppressed by electric shock and to potentiate rather than block audiogenic or pentylenetetrazol-induced seizures in rodents [10, 11, 13, 15].

Previous studies indicate that certain effects of the β-carboline inverse agonists can be blocked either by Ro 15-1788 or by benzodiazepine agonists such as diazepam [3,4], but relatively little is known about how benzodiazepine antagonists or agonists alter the effects of CGS 8216. A recent report by Shannon and Katzman [18], however, indicates that Ro 15-1788 can attenuate the decreases in suppressed responding produced by CGS 8216 in rats.

The purpose of the present study was to investigate the effects of CGS 8216 administered alone and after pretreatment with different doses of Ro 15-1788 or diazepam on schedule-controlled behavior of squirrel monkeys. An additional purpose of the study was to determine whether the behavioral effects of CGS 8216 could be altered by the α_2-adrenergic agonist clonidine, as recent studies have shown that clonidine can block some aspects of the anxiety-like syndrome induced by β-CCE in rhesus monkeys [4,14]. Our

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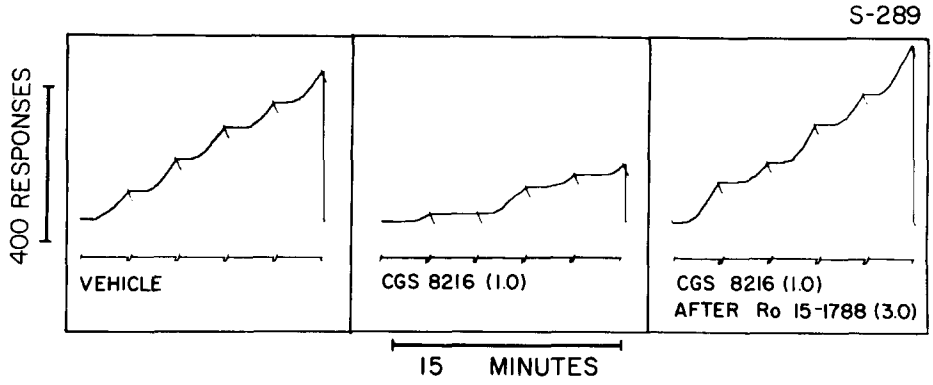

FIG. 1. Representative cumulative records of responding under the FI schedule of food presentation (monkey S-289). The records show the effects of vehicle-control, CGS 8216, or CGS 8216 administered after pretreatment with Ro 15-1788; doses (in mg/kg) are shown in parentheses. Abscissa: time. Ordinate: cumulative lever-pressing responses. The event pen (lower tracing in each record) was up during the FI and down during brief timeouts. Diagonal marks of the response pen show delivery of food. Each record shows a single component of five consecutive FIs.

results show that CGS 8216 has effects on schedule-controlled behavior that are generally opposite to those of diazepam and that these effects can be attenuated by Ro 15-1788. There was no evidence, however, that the effects of CGS 8216 were altered by either diazepam or clonidine.

METHOD

Subjects

Four adult male squirrel monkeys *(Saimiri sciureus)*, weighing 0.9–1.0 kg, were studied in daily sessions (Monday–Friday). Between sessions, the monkeys lived in individual home cages and were maintained at 85–90% of their free-feeding body weights by regulated access to food (Purina Monkey Chow, Teklad Monkey Diet, fresh fruit and vegetables); water was available ad lib. Each monkey had a chronic venous catheter implanted using the surgical procedures described previously [8]. Briefly, one end of a polyvinyl chloride catheter (inside diameter, 0.38 mm; outside diameter, 0.76 mm) was passed by way of a femoral or jugular vein to the level of the right atrium. The distal end of the catheter was passed under the skin and out between the scapulae. Catheters were flushed with 0.9% saline solution and sealed with stainless steel obturators when not in use. The monkeys wore nylon mesh jackets at all times to protect the catheters. Monkeys S-289, S-347 and S-350 had been studied previously under a fixed-interval (FI) schedule similar to the one described below and had received acute injections of benzodiazepine agonists and antagonists [24,25]. Monkey S-351 was experimentally naive at the beginning of the study.

Apparatus

During experimental sessions, monkeys sat in Plexiglas chairs within ventilated, sound-attenuating chambers, that were provided with white noise to mask extraneous sounds [21]. A response lever was mounted on a transparent wall in front of the monkey. Each press of the lever with a minimal downward force of 0.25 N produced an audible click within the chamber and was recorded as a response. Two red light bulbs could be illuminated to serve as a visual stimulus. Food pellets (190 mg; Formula L., Noyes Co., Lancaster, NH) could be delivered to a tray in the front wall of the chair.

Behavioral Procedures

Monkeys were trained to respond under a 3-min FI schedule of food presentation. In the presence of a red light, the first response after 3 min produced a pellet of food followed by a brief (10-sec) timeout period. During the timeout, the chamber was dark and responses had no scheduled consequences. If a response was not made within 60 sec after the 3-min FI elapsed, the 10-sec timeout started automatically without presentation of food. Daily experimental sessions consisted of four sequential components, each of which was made up of five consecutive FIs. Each component of five FIs was preceded by an extended (15-min) timeout period, during which drugs could be injected as described below. Daily sessions lasted approximately two hours.

Drugs and Injection Procedures

CGS 8216 was dissolved in small amounts of 95% ethanol, propylene glycol, 1.0 N sodium hydroxide and Emulphor EL-620P (GAF Corp., New York, NY); diazepam and Ro 15-1788 were dissolved in small amounts of 95% ethanol and Emulphor EL-620P; and clonidine HCl was dissolved in 0.9% saline. Solutions of each drug were further diluted with 0.9% saline to the desired concentrations. Each dose was infused through the venous catheter in a volume of 0.6 ml/kg body weight or less, followed by a 0.7 ml infusion of 0.9% saline to flush the catheter. Control infusions were similar volumes of the drug vehicles followed by a saline flush. Infusions of CGS 8216, diazepam and Ro 15-1788 contained less than 0.05 ml of either ethanol or propylene glycol, amounts which had no systematic effects on responding in vehicle-control experiments.

Drugs were studied using a cumulative dosing procedure identical to the one described by Wettstein and Spealman [24,25]. Briefly, incremental doses were infused IV 5 min after the start of each 15-min timeout period, permitting determination of a four-point cumulative dose-effect curve during a single test session. In some experiments, only three cumulative doses were studied and no infusion was given during the fourth timeout period. In these instances, data from the fourth FI component were not included in analysis of results. Each test session was preceded by a control ses-

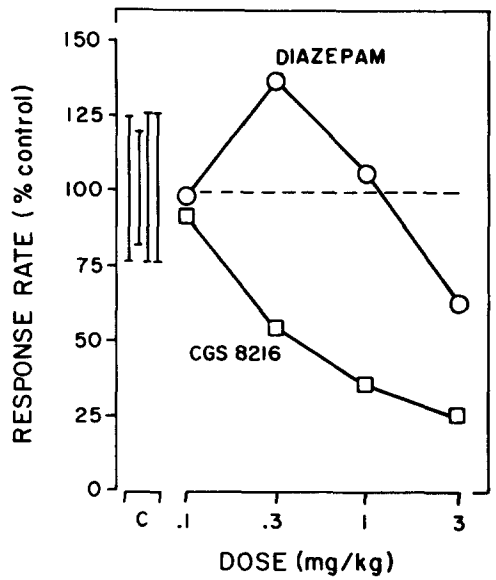

FIG. 2. Effects of CGS 8216 and diazepam under the FI schedule of food presentation. Abscissa: cumulative dose, log scale. Ordinate: response rate expressed as percent of control. Points are means based on one to three determinations in each of four monkeys. Lines with brackets at "C" show the 99% confidence limits of the mean vehicle-control response rates in each of the four sequential FI components for the group of monkeys.

sion during which rates and patterns of responding were stable. Usually, one cumulative dose-effect curve was determined per week. In experiments with drug combinations, selected doses of Ro 15-1788, diazepam or clonidine were injected IV immediately before the session, and incremental doses of CGS 8216 were injected during the session as described above. Drugs and drug combinations were studied in different orders with different monkeys.

Measurement of Drug Effects

Rates of responding were calculated separately in each of the four sequential components of the session by dividing the total number of responses in a component by the total time the component was in effect. For individual subjects, mean control rates of responding in each component were determined by averaging data from all vehicle-control sessions that preceded drug test sessions, 99% confidence limits of the means were calculated. The effect of each dose or dose combination was expressed as a percentage of the mean response rate in the corresponding component during control sessions. The effects in individual subjects were considered significant when the mean rate of responding after drug was beyond the 99% confidence limits for response rate during vehicle-control sessions for that monkey. Analyses of variance [20] were used to compare the different treatment conditions in the groups of monkeys.

RESULTS

Control Performance

Rates of responding during vehicle-control sessions averaged 0.30 to 0.64 responses/sec for the different monkeys. Control response rates varied little across the four sequential components of the session, deviating by an average of less than 10% of the whole-session means for individual subjects. Temporal patterns of responding during control sessions were characteristic of performances under FI schedules of food presentation: low rates of responding in the early portion of the interval were followed by acceleration to higher rates later in the interval (Fig. 1, left panel).

Effects of CGS 8216 and Diazepam

CGS 8216 (0.1–3.0 mg/kg) produced dose-related decreases in responding under the FI schedule (Fig. 2, squares). Response rates were significantly reduced after the two highest doses of CGS 8216 (1.0 and 3.0 mg/kg) in each of the four monkeys studied. The large doses of CGS 8216 also disrupted normal patterns of FI responding, the most prominent effect being an extended pause at the beginning of most intervals, sometimes followed by sporadic responding as the interval progressed (Fig. 1, center panel). In contrast to CGS 8216, diazepam (0.1–3.0 mg/kg) had biphasic effects on FI responding (Fig. 2, circles). One or more intermediate doses of diazepam increased responding significantly in each monkey, whereas the highest dose decreased responding significantly in three of four monkeys.

Effects of CGS 8216 After Pretreatment With Ro 15-1788

Pretreatment with Ro 15-1788 attenuated the rate-decreasing effects of CGS 8216 in a dose-related manner (Fig. 3). Although the 1.0 mg/kg dose of Ro 15-1788 did not markedly alter the dose-effect curve for CGS 8216 (Fig. 3, filled triangles), higher doses of Ro 15-1788 (3.0 or 5.6 mg/kg) at least partially blocked the rate-decreasing effects of 1.0 or 3.0 mg/kg of CGS 8216 in each of the four monkeys (Fig. 3, filled squares and circles). In some cases (e.g., monkey S-289), rates and patterns of responding characteristic of those observed during control sessions could be fully restored by pretreatment with either 3.0 or 5.6 mg/kg of Ro 15-1788 (Fig. 1, right panel). Analysis of variance showed that the effects of CGS 8216 after pretreatment with 3.0 or 5.6 mg/kg of Ro 15-1788 were significantly different from those of CGS 8216 alone ($p=0.049$ and $p=0.003$, respectively).

Effects of CGS 8216 After Pretreatment With Diazepam or Clonidine

There was no evidence that pretreatment with diazepam (0.3–3.0 mg/kg) attenuated the rate-decreasing effects of CGS 8216. As shown in Table 1, the reductions in FI response rates produced by 1.0 or 3.0 mg/kg of CGS 8216 in combination with diazepam were similar to those produced by CGS 8216 alone. Pretreatment with clonidine (0.01 or 0.03 mg/kg) also failed to systematically attenuate the decreases in FI response rates produced by the two highest doses of CGS 8216 (Table 1). When given alone, 0.01 and 0.03 mg/kg of clonidine decreased responding to 90% and 68% of control, respectively, in the group of four monkeys (data not shown). Doses of clonidine greater than 0.03 mg/kg were not studied in combination with CGS 8216 because of their pronounced rate-decreasing effects [12].

DISCUSSION

The pyrazoloquinoline CGS 8216 produced dose-related decreases in responding by squirrel monkeys under the FI schedule of food presentation, whereas diazepam had a biphasic effect on response rate. These findings are consis-

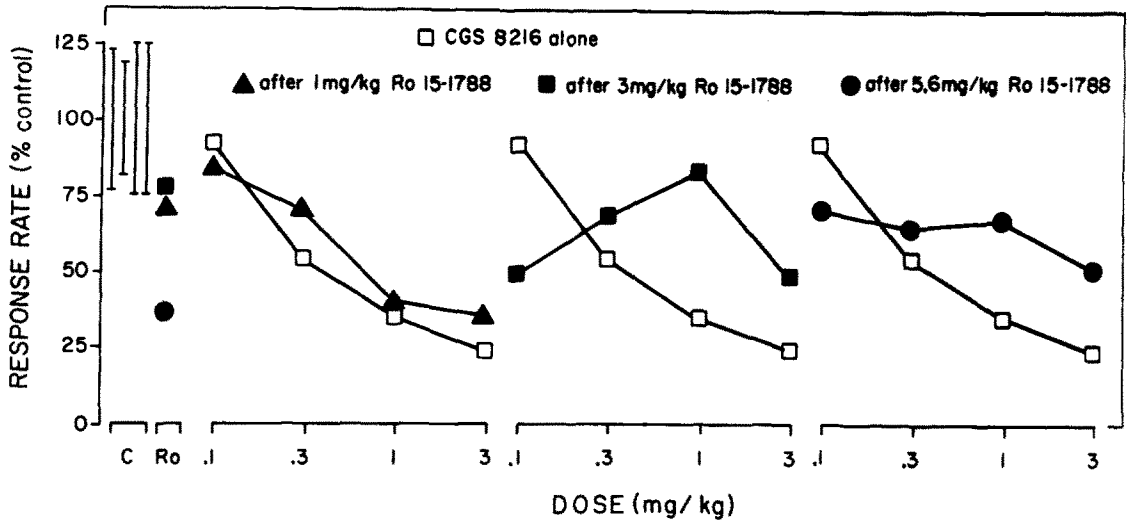

FIG. 3. Effects of CGS 8216 after pretreatment with Ro 15-1788 under the FI schedule of food presentation. Points are means based on one to three determinations in each of four monkeys. The effects of Ro 15-1788 alone (symbols at "Ro") in the same four monkeys are shown for comparison. The effects of CGS 8216 alone (open squares) are replotted from Fig. 1. Other details as in Fig. 2.

TABLE 1

EFFECTS OF CGS 8216 AFTER PRETREATMENT WITH DIAZEPAM OR CLONIDINE ON RESPONDING UNDER THE FI SCHEDULE OF FOOD PRESENTATION

Pretreatment		CGS 8216 (mg/kg)			
Drug	Dose (mg/kg)	0.1	0.3	1.0	3.0
		Responses/sec (% control)[b]			
No pretreatment[a]		88	51	33	22
Diazepam	0.3	145	85	30	30
	1.0	140	107	24	24
	3.0	—[c]	48	21	14
Clonidine	0.01	83	28	21	29
	0.03	84	59	15	14

[a]The effects of CGS 8216 alone are from Fig. 1.
[b]Data are averages based on one to three determinations in each of four monkeys.
[c]Not studied.

tent with previous reports that CGS 8216 has a profile of behavioral actions which differ qualitatively from those of benzodiazepine-like agonists. In contrast to the agonists, CGS 8216 has been found to decrease rather than increase food- or water-maintained responding under FI and FR schedules in dogs and rats and to only decrease water-maintained responding suppressed by electric shock in rats [11, 13, 18, 19]. Moreover, CGS 8216 potentiates rather than blocks audiogenic- or pentylenetetrazol-induced seizures in mice and rats and increases rather than reduces tonic muscle activity in rats [9, 10, 15].

In the present study, the decreases in response rate normally produced by high doses of CGS 8216 were either fully or partially blocked after pretreatment with 3.0 or 5.6 mg/kg of Ro 15-1788. These findings extend those of Shannon and Katzman [18], who found that Ro 15-1788 attenuated the decreases in suppressed responding produced by CGS 8216 in rats. The results of both studies are similar to those reported previously for the effects of the inverse agonist β-CCE administered in combination with Ro 15-1788. Barrett *et al.* [2], for example, found that the decreases in suppressed responding produced by β-CCE could be antagonized by pretreatment with Ro 15-1788 in squirrel monkeys, and Takada *et al.* [22] reported that the discriminative-stimulus effects of β-CCE could be blocked by Ro 15-1788 in rhesus monkeys. Taken together, our findings that CGS 8216 and diazepam had qualitatively different effects on FI responding and that the effects of CGS 8216 were attenuated by Ro 15-1788 are consistent with the view that CGS 8216 acts as a benzodiazepine inverse agonist in squirrel monkeys when studied under conditions involving schedule-controlled behavior [10,15].

Low doses of Ro 15-1788, when given alone, only had small effects on response rate, whereas the highest dose (5.6 mg/kg) decreased rate in most monkeys. There have been occasional reports which have suggested that Ro 15-1788 has inverse agonist-like effects in addition to its effects as a benzodiazepine antagonist [6, 7, 23]. It is conceivable that the decreases in response rate produced by the highest dose of Ro 15-1788 in the present study reflect such complex actions. It is noteworthy, however, that over the range of doses studied Ro 15-1788 had little or no tendency to exacerbate the decreases in FI responding produced by CGS 8216, as might have been expected if Ro 15-1788 had predominantly inverse agonist actions.

Although CGS 8216 appears to have certain inverse agonist effects in common with β-carboline derivatives such as β-CCE, some differences between the two drugs are noteworthy. Administration of CGS 8216 to squirrel monkeys in the present study did not induce convulsions at any dose, whereas β-CCE is known to induce convulsions at behaviorally active doses in this species [2,17]. Furthermore, pretreatment with diazepam (up to 3.0 mg/kg) or clonidine (up to 0.03 mg/kg) did not appreciably alter the decreases in FI responding produced by high doses of CGS 8216 in our study. These findings are consistent with those of Sanger

[16] who also found that diazepam did not attenuate the decreases in fixed-ratio responding produced by CGS 8216 in rats. In contrast, diazepam has been found to block the decreases in suppressed water licking produced by several β-carboline derivatives in rats [3], and both diazepam (1.0 mg/kg) and clonidine (0.01 mg/kg) have been found to attenuate the increases in vocalization, heart rate, blood pressure and plasma epinephrine levels produced by β-CCE in rhesus monkeys [4]. It appears, therefore, that CGS 8216 can be distinguished from inverse agonists of the β-carboline type on the basis of its effects in the presence of diazepam or clonidine.

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