Pharmacology Biochemistry & Behavior, Vol. 23, pp. 317–323, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

Pyrazoloquinoline Benzodiazepine Receptor Ligands: Effects on Schedule-Controlled Behavior in Dogs

HARLAN E. SHANNON AND WILLIAM A. THOMPSON

National Institute on Drug Abuse, Addiction Research Center, P.O. Box 5180, Baltimore, MD 21224

Received 13 September 1984

SHANNON, H. E. AND W. A. THOMPSON *Pyrazoloquinoline benzodiazepine receptor ligands: Effects on schedule-controlled behavior in dogs.* PHARMACOL BIOCHEM BEHAV **23**(2) 317–323, 1985.—The effects of diazepam and the pyrazoloquinoline benzodiazepine receptor ligands CGS8216, CGS9896 and CGS9895 on schedule-controlled responding were studied in dogs. Responding was maintained under a multiple fixed-interval (FI) 5-min fixed-ratio (FR) 30 response schedule of food presentation. Diazepam (PO) produced dose-related decreases in response rates under FR component. Under the FI, rates first increased and then decreased with increasing doses of diazepam. Diazepam also produced a dose-related disruption of the temporal pattern of responding under the FI as measured by decreases in quarter-life values. CGS8216 IV produced dose-related decreases in response rates under both components. The highest oral dose of CGS8216 also decreased rates in both components. CGS8216 was approximately 100 times more potent by the IV route as compared to the oral route. CGS9896 IV had no significant effect on responding under either component of the multiple schedule. However, with increasing doses of CGS9896 PO, response rates under both components first decreased and then returned to control values. CGS9895 PO was without significant effect on responding. When CGS8216 was administered concomitantly with graded doses of diazepam, the former drug blocked the rate-decreasing effects of diazepam under the FR component, but not the rate-increasing effects of diazepam under the FI. The present results demonstrate that although these three pyrazoloquinolines are benzodiazepine receptor ligands, they do not exhibit diazepam-like effects on schedule-controlled behavior.

Pyrazoloquinolines Diazepam Schedule-controlled behavior

THE pyrazoloquinolines CGS8216, CGS9896 and CGS9895 are potent benzodiazepine receptor ligands [8, 13, 28] but with profiles of action which differ from typical benzodiazepines such as diazepam. CGS8216 appears to be a benzodiazepine antagonist with intrinsic activity, and under some conditions may be an inverse agonist of the benzodiazepine type. CGS8216 antagonized many of the effects of diazepam but also disrupted punished responding in rats [2]. In addition, CGS8216 antagonized the anticonvulsant effects of diazepam against pentylenetetrazole [2], and also potentiated the convulsant effects of pentylenetetrazole and picrotoxin [10]. The benzodiazepine antagonist Ro 15-1788 blocked the proconvulsant effects of CGS8216 against pentylenetetrazole but not picrotoxin [10]. CGS9896 appears to be an agonist which exhibits only a portion of the pharmacologic profile of diazepam-like benzodiazepines. CGS9896 increased rates of punished responding in rats with the same maximal effect as diazepam but failed to produce rotarod ataxia [28]. CGS9895 may be a partial agonist of the benzodiazepine type since it increased rates of punished responding in rats but with a smaller maximal effect than diazepam [28], and also antagonized the discriminative effects of diazepam [24]. Further data are needed to evaluate the behavioral effects of these benzodiazepine receptor ligands.

Diazepam and chlordiazepoxide have been reported previously to increase low rates of responding under FI schedules and to decrease the high rates of responding under FR schedules of food presentation [6, 7, 27]. The purpose of the present study was to assess the effects of CGS8216, CGS9895 and CGS9896 in comparison with diazepam on rates and temporal patterns of responding maintained under a multiple fixed-interval (FI) 5-min, fixed-ratio (FR) 30 response schedule of food presentation in dogs. In addition, the dose-effect curve for diazepam was determined alone and in the presence of CGS8216 in order to evaluate the antagonist properties of the latter drug.

METHOD

Subjects

Three mature female (D3787, D3871, D3932) and two mature male (D3769, D4216) beagle dogs, obtained from commercial suppliers (Ridglan Farms, Mt. Horeb, WI or Lab Research Inc., Kalamazoo, MI) and weighing 8.6 to 12.5 kg, were used. Three dogs (D3769, D3787, D4216) had histories of IV drug self-administration under fixed-interval or second-order schedules, while the remaining two (D3871, D3932) were experimentally naive. The dogs were maintained at approximately 85 percent of their free feeding weights by food presented during the session and postsession supplemental feeding.

Dogs were individually housed in wire pens between experimental sessions and fed Purina Dog Chow and water.

Regularly scheduled physical examinations and clinical tests (urinalysis, fecal examination, complete blood count, blood chemistry analysis) were conducted throughout the experiment to monitor the health status of each dog.

Apparatus

The experiment chamber was a stainless steel canine cage enclosed in a sound and light attenuating environmental cubicle. The chamber was equipped with a ventilating fan which provided masking noise. A response lever (Model 1AF4, Micro Switch, A division of Honeywell, Freeport, IL) was mounted on a panel (30×26 cm) inside the front door of the cage at a height of 20 cm from the cage floor to the bottom of the lever. Each press of the lever with a minimal horizontal force of 200 g (1.96 N) produced an audible click of the microswitch and was recorded as a response. The panel was equipped with three sets of stimulus lights (white, green, and red) above the response lever and a set of orange stimulus lights to the left of the lever and adjacent to the bowl into which food pellets were delivered. Each response illuminated the while stimulus light above the lever for 15 msec to provide response feedback. In addition, a white, 25 watt houselight was mounted above the cage near the front and provided general illumination. A pellet dispenser (model A, Ralph Gerbrands Co, Arlington, MA) mounted on the left side of the cubicle delivered 1.0 g food pellets (Formula "H" Precision Food Pellets, P. J. Noyes Co., Lancaster, NH). A PDP8/E based SCAT 3002 system (BKP Scientific, Berlin, MA) was used to control schedule contingencies and record data.

Procedure

Dogs performed under a multiple fixed-interval 5-min fixed-ratio 30 response schedule of food presentation [9]. Each session began with a 5 min timeout, during which the chamber was dark and responses had no scheduled consequences, followed by a FI 5 min component signalled by the overhead houselight and the green stimulus light on the upper left portion of the panel. In the FI component, the first response after 5 min had elapsed resulted in the delivery of 5 food pellets accompanied by the orange light. The FR30 component was signalled by the houselight and the red light on the upper right portion of the panel. In the FR component, the 30th response resulted in the delivery of 5 food pellets accompanied by the orange light. A 60-sec limited hold was imposed in both components. Thus, after 5 min had elapsed in the FI5 min component, the dog had 60 sec to emit a response before the food was forfeited. In the FR30 component the dog had 60 sec to emit 30 responses or the food was forfeited. Schedule components alternated after each food presentation or 60 sec limited hold. A 30-sec timeout period separated components. Each session ended after the tenth FR component.

Sessions were conducted Monday through Friday with Tuesday and Friday being drug dose days and Thursday serving as a control day. Drugs were always administered 30 min prior to the session. Doses were tested in a different sequence in each dog. On control days subjects received lactose-filled capsules or the vehicle or both 30 min before the session.

Drugs

CGS8216, CGS9895, and CGS9896 were gifts from CIBA–Geigy (Summit, NJ) and administered orally in gelatin capsules or intravenously in a 60 percent propyleneglycol, 20 percent ethanol, 20 percent distilled water (v/v/v) vehicle. Diazepam, a generous gift from Hoffmann-LaRoche Inc. (Nutley, NJ), was administered orally in gelatin capsules. Drugs were always administered 30 min prior to the session.

Data Analysis

Overall rates of responding for the FI 5 min and FR 30 components were computed each session by dividing the total number of responses in the presence of the appropriate stimulus light by the total time the light was illuminated. Drug data are expressed as a percent of the mean response rate for each dog during control sessions for each drug series. Average rates of responding during the timeouts were calculated by dividing the total number of responses during the timeouts by the total timeout time during the entire session. The temporal pattern of responding for the FI 5 min component was analyzed by dividing each interval into 10 successive 30-sec segments. The total number of responses in each segment were accumulated over the entire session. From these measures the percentage of the interval required to complete the first quarter of the responses was computed by linear interpolation. Thie value, which yields an index of the temporal pattern of responding relatively independent of response rate, is termed quarter-life [14,16]. A rate-dependency analysis was completed with drug rates plotted as a function of control rates [5]. Regression lines were calculated for each dose by the method of least squares.

Differences between dose-effect curves were determined using standard bioassay analysis of variance techniques. Except as noted in Results, all assays satisfied the requirements of a significant mean square for regression with nonsignificant mean squares for nonparallelism, preparations differences and deviations from linearity. Comparison of treatment and control means were made using one-way analysis of variance and a Dunnett's test.

RESULTS

Control Performance

Rates and temporal patterns of responding during control sessions were similar to the performance engendered under multiple FI FR schedules in a variety of species [4, 9, 15, 26]. Performance under the FI component was characterized by low rates of responding early in the interval followed by a gradual increase to high rates as the interval progressed. Under the FR component, performance was characterized by an initial pause followed by responding at a high, steady rate until food presentation. Control rates of responding under the FI component varied in individual dogs from 0.12 to 0.85 responses/sec and quarter-life values varied from 51 to 74 percent. Under the FR component, control rates varied from 1.2 to 3.2 responses/sec in individual dogs. Responding during timeout periods always averaged less than 0.05 responses/sec.

Acute Drug Effects

Diazepam (PO) produced dose-related decreases in response rates under the FR component of the multiple schedule (Fig. 1). In contrast, rates under the FI component generally were increased. Also, there was a dose-related decrease in the FI quarter-life value, indicating that a greater proportion of the total responses were occurring early in the FI as the dose of diazepam increased.

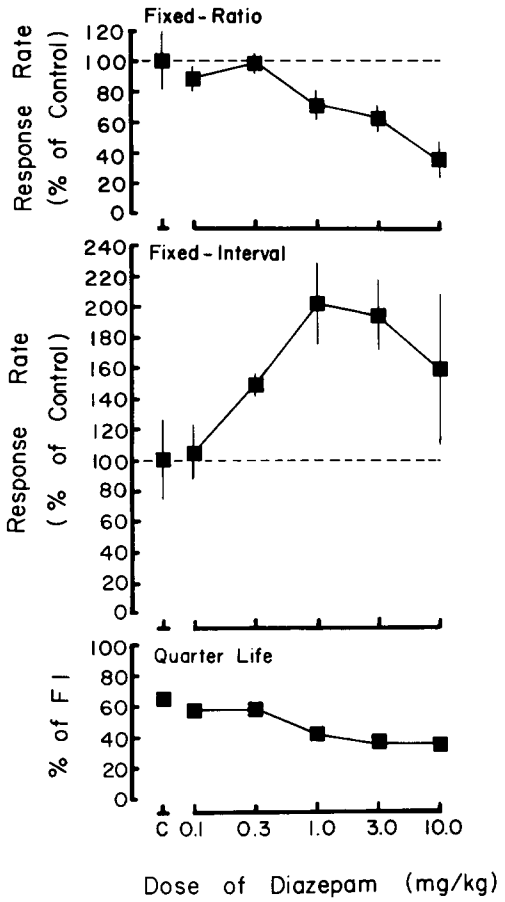

FIG. 1. Effects of diazepam PO on average rates of responding under an FR 30 schedule component (top), FI 5-min component (middle), and on quarter-life values during the FI 5-min component (bottom) in dogs. Abscissa: dose of drug (mg/kg), log scale. Ordinates: mean rates of responding expressed as a percentage of control values (top and middle) and quarter-life values expressed as a percentage of the interval (bottom). Points above C represent mean control (placebo capsule) values, 100 percent, based on 2 or 3 determinations in each dog. Other points are the mean on one determination in each of 4 dogs. The vertical lines represent ±1 SEM and are absent when this value is less than the size of the point.

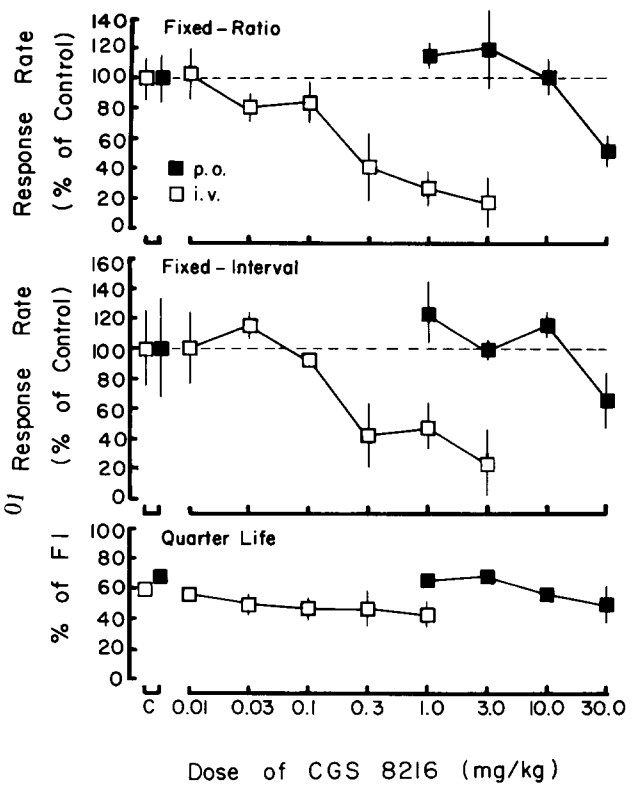

FIG. 2. Effects of CGS8216 PO and IV on average rates of responding under an FR 30 schedule component (top), FI 5-min component (middle), and on quarter-life values during the FI 5-min component (bottom) in dogs. Abscissa: dose of drug (mg/kg), log scale. Ordinates:mean rates of responding expressed as a percentage of control values (top and middle) and quarter-life values expressed as a percentage of the interval (bottom). Points above C represent mean control (placebo capsule or drug vehicle) values, 100 percent, based on 2 or 3 determinations in each dog. Other points are the mean of one determination in each of 4 dogs. The vertical lines represent ±1 SEM and are absent when this value is less than the size of the point.

CGS8216, administered PO, had little effect on responding under either schedule component over the dose-range of 1.0 to 10 mg/kg (Fig. 2). However, 30 mg/kg PO significantly (Dunnett's test, $p<0.05$) decreased rates of responding under both the FR and FI components; the quarter-life value was also decreased somewhat. On the other hand, intravenous administration of CGS8216 produced a significant dose-related decrease in response rates under both the FR and FI components; the quarter-life value also decreased in a dose-related manner, but these effects were not statistically significant.

With increasing doses of CGS9896 (PO), response rates first decreased and then returned to control values under both the FR and FI schedule components (Fig. 3). Under the FR component, doses of 0.1 to 1.0 mg/kg PO produced dose-related decreases in rates to approximately 50 percent of control. The 1.0 mg/kg dose decreased rates in all 4 dogs, and this decrease was statistically significant (Dunnett's test, $p<0.05$). Rates were comparable to control values after doses of 3.0 to 30 mg/kg PO. Under the FI component, rates were reduced to approximately 70 percent of control by doses of 0.3 to 3.0 mg/kg PO, but were comparable to control values after 10 to 30 mg/kg PO. Quarter-life values were not significantly altered by CGS9896 given PO. When administered IV, CGS9896 (0.3 to 10 mg/kg) had no significant effect on response rates under either schedule component, nor were quarter-life values altered. However, the lowest dose of CGS9896 administered IV (0.1 mg/kg) tended to decrease rates in both schedule components and it is possible that complex effects, similar to those observed with oral drug administration, might have been observed with IV administration had lower doses been tested.

CGS9895, administered PO, had no effect on response-rates under either schedule component or on the FI quarter-life value over the dose-range of 0.1 to 10 mg/kg (Fig. 4). A dose of 30 mg/kg decreased rates under both components but

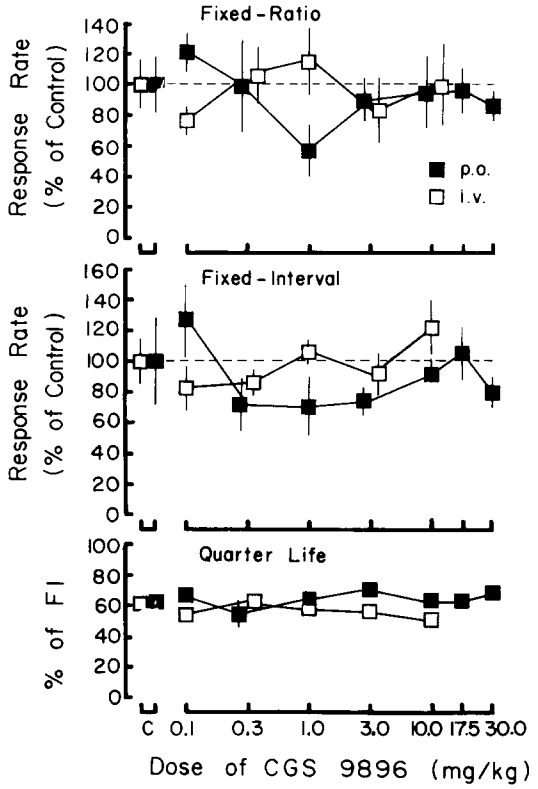

FIG. 3. Effects of CGS9896 PO and IV on average rates of responding under an FR 30 schedule component (top), FI 5-min component (middle), and on quarter-life values during the FI 5-min component (bottom) in dogs. Abscissa: dose of drug (mg/kg), log scale. Ordinates: mean rates of responding expressed as a percentage of control values (top and middle) and quarter-life values expressed as a percentage of the interval (bottom). Points above C represent mean control (placebo capsule or drug vehicle) values based on 3 determinations in each dog. Other points are the mean of one determination in each of 4 dogs. The vertical lines represent ±1 SEM and are absent when this value is less than the size of the point.

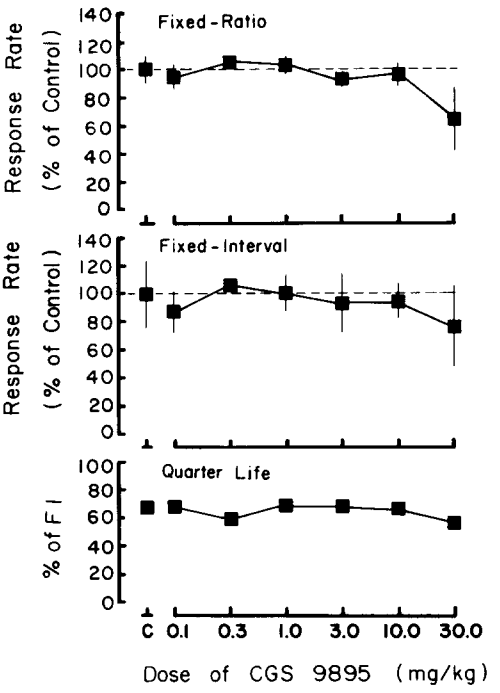

FIG. 4. Effects of CGS9895 PO on average rates of responding under an FR 30 schedule component (top), FI 5-min component (middle), and on quarter-life values during the FI 5-min component (bottom) in dogs. Abscissa: dose of drug (mg/kg), log scale. Ordinates: mean rates of responding expressed as a percentage of control values (top and middle) and quarter-life values expressed as a percentage of the interval (bottom). Points above C represent mean control (placebo capsule) values based on 3 determinations in each dog. Other points are the mean of one determination in each of 4 dogs. The vertical lines represent ±1SEM and are absent when this value is less than the size of the point.

had no effect on the quarter-life value. Higher doses were not tested due to a limited drug supply. CGS9895 was not tested IV due to solubility limitations.

Rate-Dependency

The effects of diazepam under the FI component were dependent on the control rate of responding (Fig. 5, upper left panel); low rates were increased while high rates were increased less or decreased. CGS9896 (Fig. 5, right panels) did not produce effects which were consistently dependent upon control rates of responding when compared across the two routes of administration. There were no dose-related changes in the slopes of the regression lines, nor were the regression lines shifted along the abscissa. CGS9895 (Fig. 5, lower left panel) tended to increase low rates and also decrease high rates of responding, but this effect was not observed consistently in all dogs. CGS8216 (Fig. 5, middle panels) tended to increase low rates of responding but decreased high rates, particularly at the highest doses.

Interactions Between Diazepam and CGS8216

Administered alone, diazepam PO produced effects (Fig. 6) virtually identical to those described above for diazepam. In the FR component, 3.0 and 10 mg/kg of CGS8216 PO blocked the rate-decreasing effects of diazepam. Administered concomitantly with 3.0 mg/kg of CGS8216, diazepam produced a slight increase in FR response rates. In the FI component, the increase in response rates produced by diazepam was significantly greater in the presence of 3.0 mg/kg CGS8216 as evidenced by a significant preparations term in the bioassay analysis, but the peak-effect dose of diazepam (3.0 mg/kg) was unchanged. A dose of 10 mg/kg of CGS8216 had no significant affect on the diazepam dose-effect curve in the FI component. The dose-related decreases in quarter-life values produced by diazepam were unaffected by either dose of CGS8216.

DISCUSSION

Diazepam (PO) only increased rates of responding under the FI component but decreased rates under the FR component of a multiple schedule in dogs. Qualitatively similar results were previously reported for chlordiazepozide in squirrel monkeys [7]. In the only previous study assessing the effects of diazepam on performance under a multiple FI

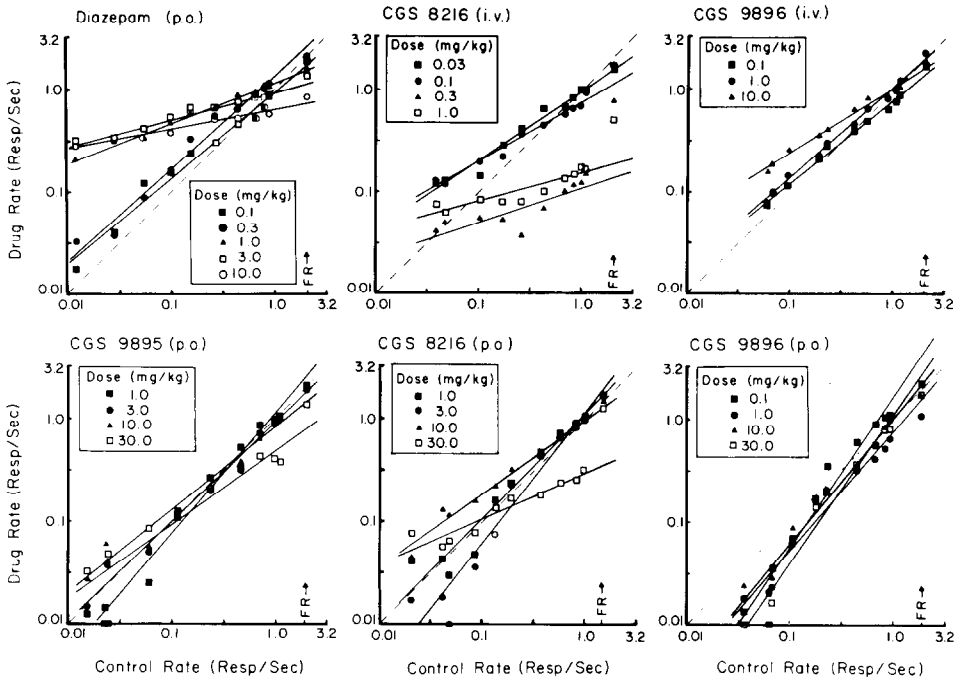

FIG. 5. Average effects of diazepam and the three pyrazoloquinolines on the local rates of responding during successive tenths of the FI 5-min component and during the FR 30 component plotted as a function of the average control rate of responding. Abscissa: control rate, log scale. Ordinate: rate after drug administration, log scale. The dashed line indicates no change from control data. Linear regression lines were fit to the data from the FI component by the method least squares. The data from the FR component are indicated by the arrow in each panel.

FR schedule, Bignami and Gatti [3] reported that diazepam, as well as chlordiazepoxide, produced inconsistent effects in pigeons. However, benzodiazepines generally have been reported to increase FI responding in rats [21], cats [20], pigeons [27] and squirrel monkeys [1] when FI performance was studied either in isolation or as one component of a multiple schedule which also included a punishment component. Also consistent with the present results, benzodiazepines generally have been reported to decrease FR responding in rats [6,22] and squirrel monkeys [17].

Unlike diazepam, CGS8216 decreased rates in both components of the mutiple schedule by the IV route and at the highest oral dose. Doses of 0.3 mg/kg IV and 30 mg/kg PO were approximately equieffective in decreasing rates in both components. Thus, CGS8216 was approximately 100 times more potent by the IV as compared to the oral route. CGS8216 previously has been reported to affect behavior, including disruption of punished responding in rats [2,18], reduction of social interactions in rats [11], and potentiation of the convulsant effects of pentylenetetrazole and picrotoxin in mice [10]. Taken together, these results indicate that CGS8216 has intrinsic activity. Some of these actions of CGS8216, such as potentiation of pentylenetetrazole, are opposite those of diazepam and are blocked by the selective benzodiazepine antagonist Ro 15-1788 [10]; these actions thus appear to be inverse agonist properties. On the other hand, the potentiation of picrotoxin by CGS8216 is not blocked by Ro 15-1788 and therefore dose not represent an inverse agonist effect. In the present study, the effects of CGS8216 were not entirely opposite those of diazepam, and therefore it is unlikely that CGS8216 functioned as an inverse agonist at benzodiazepine receptors in disrupting schedule controlled performance.

By the intravenous route, CGS9896 was without significant effect over the dose-range tested. By the oral route, moderate doses of CGS9896 produced modest (30 to 50 percent) decreases in rates under both components of the multiple schedule; higher doses did not significantly alter response rates. The reason for this nonmonotonic effect is presently unclear. Similarly, the reason for the lack of effect by the IV route is unclear, but might be due either to the failure to test sufficiently low doses IV, or to differences in metabolism by the two routes. However, the modest magnitude of the effect by the oral route and the apparent lack of concordance in the effects by the two routes suggests the results obtained with oral administration should be interpreted with caution and await confirmation in further experiments. Nevertheless, CGS9896 did not produce diazepam-like effects on performance under a multiple FI FR schedule. These results are in accord with previous reports that the profile of action of CGS9896 differs from that of diazepam. This pyrazoloquinoline also did not produce ataxia as measured on the rotarod in mice [28] nor diazepam-like discriminative effects in rats [24]. On the other hand, CGS9896, like diazepam, increased rates of punished responding in rats and blocked the convulsant effects of pentylenetetrazole in mice [28]. Taken together, these results suggest that CGS9896 is a selective ligand for a subpopulation of benzodiazepine receptors [24].

Oral CGS9895 also was without significant effect on response rates over the dose-range tested. In contrast, CGS9895 has been reported to increase rates of punished responding, but with a smaller maximal effect than

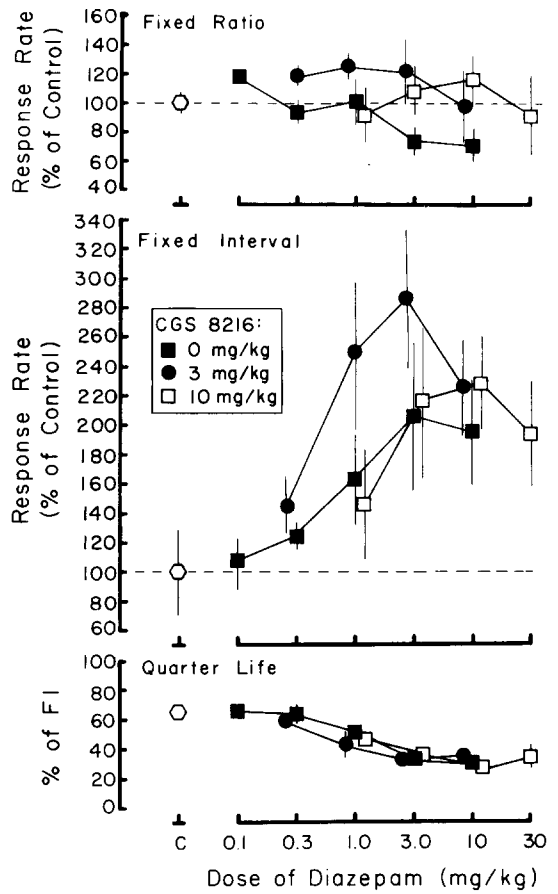

FIG. 6. Effects of diazepam PO administered alone and concomitantly with CGS8216 PO on average rates of responding under the FR 30 schedule component (top), FI 5-min component (middle), and on quarter-life values during the FI 5-min component (bottom) in dogs. Abscissa: dose of diazepam (mg/kg), log scale. Ordinates: mean rates of responding expressed as a percentage of control values (top and middle) and quarter-life values expressed as a percentage of interval (bottom). Points above C represent mean control (placebo capsules) values, 100 percent, based on 6 determinations in each dog. Other points are the mean of one determination in each of 4 dogs. The vertical lines represent ±1 SEM and are absent where this value is less than the size of the point.

diazepam, and also to block pentylenetetrazole-induced convulsions [28]. Moreover, at higher doses, CGS9895 antagonized the anticonvulsant effects of diazepam in mice [28] and also the discriminative effects of diazepam in rats [24]. The antagonist activity of CGS9895 was not evaluated in the present study due to a limited drug supply. However, CGS9895 does antagonize the effects of diazepam on performance under a multiple FI FR schedule in rats (Katzman and Shannon, unpublished observations). This profile of activity is not entirely consistent with the interpretation that CGS9895 is a partial agonist. Rather, together with previous reports, these data suggest that CGS9895 is an agonist (or partial agonist) at one subpopulation of benzodiazepine receptors and an antagonist at a different subpopulation of receptors [24].

The interactions between CGS8216 (PO) and diazepam (PO) were complex. CGS8216 antagonized the rate-decreasing effects of diazepam under the FR component in a dose-related manner. These findings are consistent with previous reports that CGS8216 antagonized the anti-conflict, anticonvulsant and ataxia-producing properties of diazepam [2,19] as well as the discriminative effects of diazepam [23,35]. Under the FI component, however, the rate-increasing effects of diazepam were potentiated by the 3.0 mg/kg dose but were largely unaffected by the 10 mg/kg dose of the antagonist. Further, neither dose of CGS8216 blocked the decreases in the quarter-life value produced by diazepam. These latter findings suggest the possibility that at doses which do not effect behavior, CGS8216 may selectively antagonize the rate-decreasing effects of diazepam, whereas higher doses, which may disrupt performance when given alone, are required to antagonize the rate increasing effects of diazepam. However, in another study in dogs responding under a similar multiple schedule (Risner and Shannon, unpublished observations) but where tones plus cue lights served as the discriminative stimuli for each component and the manipulandum was a floor-mounted lever rather than the wall-mounted lever used here, CGS8216 administered either PO or IV had no significant effect on performance. Under these latter experimental conditions (Risner and Shannon, unpublished). CGS8216 PO and IV blocked the rate-increasing effects of diazepam under the FI component as well as its rate-decreasing effects under the FR component. Thus, interactions between CGS8216 and diazepam are complex and depend critically upon a number of environmental factors and response topography.

Several investigators have previously reported that the effects of benzodiazepines are dependent on control rates of responding (e.g., [6, 7, 27]). In the present study, diazepam increased the low rates of responding which occurred early in the interval and increased less or decreased the high rates which occurred late in the interval. Under the FR component, rates were decreased by diazepam less than would have been predicted from the rates generated under the FI component. On the other hand, CGS8216 primarily decreased the high rates which occurred late in the interval while having no effect or slightly increasing low rates which occurred early in the interval; FR rates were decreased less than would have been predicted from the changes in FI rates. Thus, under the FI schedule, the effects of diazepam were generally opposite those of CGS8216. However, both drugs had similar effects under the FR schedule.

In summary, although CGS9896, CGS9895 and CGS8216 all displace [^{3}H]diazepam and are more potent than diazepam as receptor ligands, they do not produce diazepam-like effects on schedule-controlled behavior in dogs. Together with previous reports (see above), CGS9896 appears to exhibit only a portion of the pharmacologic and behavioral profile of diazepam-like drugs, suggesting that CGS9896 may be a selective agonist at a subpopulation of benzodiazepine receptors. CGS9895 has both agonist and antagonist properties in other procedures (e.g., [28]), but is relatively ineffective in disrupting schedule-controlled performance (this report). Further research is required to elucidate the profile of action of this compound. CGS8216 antagonizes most of the actions of benzodiazepines (e.g., [2]), and also disrupts schedule controlled performance. Further research is required to determine whether this latter activity of CGS8216 is due to antagonism of an endogenous benzodiazepine ligand, inverse agonist activity, or to some other mechanism of action. The latter possibility appears more likely since both CGS8216 and CGS9895 are benzodiazepine antagonists, but only

CGS8216 disrupted schedule-controlled performance, and the effects of CGS8216 were not entirely opposite those of diazepam.

ACKNOWLEDGEMENTS

The authors thank Ms. Donna Shelton and Ms.Wanda Roberts for an outstanding service in preparing this manuscript.

REFERENCES

1. 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.
2. Bernard, P., K. Bergen, R. Sobiski and R. D. Robson. CGS8216 (2-phenylprazolo[4, 3-c] quinolin-3(5H)-one, an orally effective benzodiazepine antagonist. *Pharmacologist* **23:** 150, 1981.
3. Bignami, G. and G. L. Gatti. Analysis of drug effects on multiple fixed ratio 33-fixed interval 5 min in pigeons. *Psychopharmacologia* **15:** 310–332, 1969.
4. Byrd, L. D. Contrasting effects of morphine on schedule-controlled behavior in the chimpanzee and baboon. *J Pharmacol Exp Ther* **193:** 861–869, 1975.
5. Byrd, L. D. Quantitation in behavioral pharmacology. In: *Advances in Behavioral Pharmacology*, vol 3, edited by T. Thompson, P. B. Dews and W. A. McKim. New York: Academic Press, 1981, pp. 75–109.
6. Canon, J. G. and A. S. Lippa. Effects of clozapine, chlorpromazine and diazepam upon adjunctive and schedule controlled behaviors. *Pharmacol Biochem Behav* **6:** 581–587, 1977.
7. Cook, L. Effects of drugs on operant conditioning. In: *CIBA Foundation Symposium on Animal Behavior and Drug Action*, edited by H. Steinberg, A. V. S. de Reuck and J. Knight. London: Churchill, 1964, pp. 23–40.
8. Czernik, A. J., B. Petrack, H. J. Kalinsky, S. Psychoyos, W. D. Cash, C. Tasi, R. K. Rinehart, F. R. Granat, R. A. Lovel, D. E. Brundish and R. Wade. CGS8216: receptor binding characteristics of a potent benzodiazepine antagonist. *Life Sci* **30:** 363–372, 1982.
9. Ferster, C. B. and B. F. Skinner. *Schedules of Reinforcement*. New York: Appleton-Century-Crofts, 1957.
10. File, S. E. Proconvulsant action of CGS8216. *Neurosci Lett* **35:** 317–320, 1983.
11. File, S. E. and R. G. Lister. Quinolines and anxiety: Anxiogenic effects of CGS8216 and partial anxiolytic profile of PK9084. *Pharmacol Biochem Behav* **18:** 185–188, 1983.
12. Finney, D. J. *Statistical Methods in Biological Assay*. London: Griffin, 1971.
13. Gee, K. W. and H. I. Yamamura. A novel pyrazoloquinoline that interacts with brain benzodiazepine receptors: characterization of some *in vitro* and *in vivo* properties of CGS9896. *Life Sci* **30:** 2245–2252, 1982.
14. Gollub, L. R. The relation among measures of performance on fixed-interval schedules. *J Exp Anal Behav* **7:** 337–343, 1964.
15. Gonzalez, F. A. and S. R. Goldberg. Effects of cocaine and *d*-amphetamine on behavior maintained under various schedules of food presentation in squirrel monkeys. *J Pharmacol Exp Ther* **201:** 33–43, 1977.
16. Herrnstein, R. J. and W. H. Morse. Effects of pentobarbital on intermittently reinforced behavior. *Science* **125:** 929–931, 1957.
17. Katz, J. L. and J. E. Barrett. Ethanol, pentobarbital and chlordiazepoxide effects in squirrel monkeys responding under fixed-ratio food presentation and stimulus-shock termination schedules. *Psychopharmacology (Berlin)* **56:** 153–155, 1978.
18. Mendelson, W. B., T. Davis, S. M. Paul and P Skolnick. Do benzodiazepine receptors mediate the anticonflict action of pentobarbital. *Life Sci* **32:** 2241–2246, 1983.
19. Patel, J. B, C. Martin and J. B. Malick. Differential antagonism of the anticonflict effects of typical and atypical anxiolytics. *Eur J Pharmacol* **86:** 295–298, 1983.
20. Richelle, M. Combined action of diazepam and d-amphetamine on fixed-interval performance in cats. *J Exp Anal Behav* **12:** 989–998, 1969.
21. Richelle, M., B. Xhenseval, O. Fontaine, and L. Thone. Action of chlordiazepoxide on two types of temporal conditioning in rats. *Int J Neuropharmacol* **1:** 351–391, 1962.
22. Sanger, D. J. and D. E. Blackman. Rate-dependence and the effects of benzodiazepines. In: *Advances in Behavioral Pharmacology*, vol 3, edited by T. Thompson, P. B. Dews and W. A. McKinm. New York: Academic Press, 1981,pp. 1–20.
23. Shannon, H. E. and S. L. Davis. CGS8216 noncompetitively antagonizes the discriminative effects of diazepam in rats. *Life Sci* **34:** 2589–2596, 1984.
24. Shannon, H. E. and S. Helring. Antagonism of the discriminative effects of diazepam by pyrazoloquinolines in rats. *Eur J Pharmacol* **92:** 155–157, 1983.
25. Shannon, H. E. and S. Herling. Discriminative stimulus effects of diazepam in rats: evidence for a maximal effect. *J Pharmacol Exp Ther* **227:** 160–166, 1983.
26. Waller, M. B. Effects of chronically administered chlorpromazine on multiple-schedule performance. *J Exp Anal Behav* **4:** 351–359, 1961.
27. Wuttke, W. and R. T. Kelleher. Effects of some benzodiazepines on punished and unpunished behavior in the pigeon. *J Pharmacol Exp Ther* **172:** 397–405, 1970.
28. Yokoyama, N., B. Ritter and A. D. Neubert. 2-Arylpyrazolo[4,3-*c*] quinolin-3-ones: Novel agonist, partial agonist, and antagonist of benzodiazepines. *J Med Chem* **25:** 337–339, 1982.