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Differential Interactions Between Chlordiazepoxide, Pentobarbital and Benzodiazepine Antagonists Ro 15-1788 and CGS 8216 in a Drug Discrimination Procedure

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DE VRY, J AND J L SLANGEN *Differential interactions between chlordiazepoxide, pentobarbital and benzodiazepine antagonists Ro 15-1788 and CGS 8216 in a drug discrimination procedure* PHARMACOL BIOCHEM BEHAV 24(4) 999–1005, 1986 —Rats were trained to discriminate either chlordiazepoxide (CDP, 4 mg/kg, IP, N=8) or pentobarbital (PB, 10 mg/kg, IP, N=8) from saline in a two-lever food-reinforced procedure CDP and PB dose-dependently substituted for each other (≥90% drug lever responses), indicating that their discriminative stimulus properties were closely similar However, discriminative stimulus control induced by CDP and PB differentially was affected by the proposed benzodiazepine (BDZ) antagonists Ro 15-1788 (0 08–20 mg/kg, IP) and CGS 8216 (2 5–20 mg/kg, IP) in each experimental group, suggesting that the discriminative stimulus properties of CDP and PB are mediated by different mechanisms of action When administered alone, Ro 15-1788 (5 and 20 mg/kg), but not CGS 8216, induced CDP like discriminative effects, suggesting that Ro 15-1788 may have partial (BDZ like) agonist properties, not shown by CGS 8216 Additional evidence for a behavioral difference between Ro 15-1788 and CGS 8216 is suggested by differential effects of both compounds on response rate The results may reflect differential interactions of the compounds with the BDZ receptor-GABA receptor-Cl^- ionophore complex

Drug discrimination Chlordiazepoxide Pentobarbital Benzodiazepine antagonist Ro 15-1788 CGS 8216 Rat

THE prototypical benzodiazepine (BDZ) compound chlordiazepoxide (CDP) and the barbiturate pentobarbital (PB) are able to act as discriminative stimuli in the rat [1]. In a food-reinforced two-lever drug discrimination procedure, CDP and PB substitute for each other, regardless of which type of drug is used as training drug and regardless of the training dose level ([2,15], De Vry and Slangen, unpublished results). It therefore is suggested that the discriminative stimulus (DS) properties of CDP and PB are closely similar under these experimental conditions.

In the present study it is investigated whether the DS properties of both drugs can be differentiated by the use of BDZ receptor antagonists. Ro 15-1788, an imidazodiazepine, and CGS 8216, a pyrazoloquinoline, are proposed BDZ receptor antagonists, as they inhibit the binding of BDZs to BDZ receptors; they antagonize characteristic effects of BDZ compounds and they apparently lack these BDZ effects in the effective antagonist dose range [3, 10, 13]. Because the behavioral effects of CDP (and other BDZ compounds) are thought to result from an interaction with BDZ receptors [18], it is to be expected that rats, trained to discriminate CDP from saline, will show saline appropriate behavior when sufficiently high doses of a BDZ antagonist drug are co-administered with the training drug. Similarly, it may be expected that training drug appropriate behavior induced by a substituting dose of CDP in PB trained rats, will dose-dependently shift into saline appropriate behavior when increasingly higher doses of a BDZ antagonist are co-administered with CDP. Barbiturates apparently have no affinity for the BDZ receptor [18] It is therefore to be expected that training drug appropriate behavior induced by PB, in PB trained animals as well as in CDP trained animals, will not be affected by co-administration of a BDZ antagonist with PB

Selective effects of Ro 15-1788 and CGS 8216 on discriminative responding induced by PB and the BDZ compound diazepam have been obtained in a shock avoidance drug discrimination procedure [4, 11, 20]. In rats trained to discriminate PB from saline in a milk-reinforced operant task, it has been shown that discriminative effects of CDP and diazepam, but not of PB and barbital, were affected by co-administration of Ro 15-1788 [24]. In a food-reinforced drug discrimination procedure, Ro 15-1788 also was found to selectively reverse antagonism of the pentylenetetrazol

stimulus by diazepam and des-methylclobazam, but not by PB [8]

In the present study, two groups of rats were trained to discriminate either CDP or PB from saline in a two-lever food-reinforced operant procedure, and it was tested whether Ro 15-1788 and CGS 8216 could selectively reverse the discriminative effects of CDP and PB in both groups The BDZ antagonists also were tested for possible CDP or PB like discriminative effects, as it has been reported that Ro 15-1788 may generalize to the BDZs chlorazepate [4] and CDP [6]

METHOD

Animals

Sixteen male Wistar rats (CPB-TNO, Zeist, The Netherlands), weighing 230–270 g at the beginning of the experiment, were individually housed under a non-reversed 12 hr light-dark cycle and a room temperature of 20–22°C Tap water was freely available. Laboratory food (13 g) was available during a 2 hr period, beginning 1 hr after each daily session Food was freely available from Friday afternoon until Sunday morning

Apparatus

Four ventilated rat chambers equipped with two retractable levers were used. A pellet dispenser delivered 45 mg pellets (Noyes) in a tray placed between the levers During sessions, both levers were in the chambers and the central houselight was illuminated; white noise (70 dB) was continuously present

Discrimination Training

After habituation to the laboratory conditions, all rats were trained to lever-press according to a fixed ratio 10 schedule of reinforcement (FR 10, reinforcement after every tenth press on the appropriate lever), thereafter daily discrimination training was started. Two experimental groups were used in this study. group CDP (N=8) had to discriminate 4 mg/kg CDP (IP, t−15 min) from saline, group PB (N=8) had to discriminate 10 mg/kg PB (IP, $t-15$ min) from saline. Depending on the injection condition (drug or saline), reinforcement could be obtained by pressing either the "drug appropriate" lever (D lever) or the "saline appropriate" lever For half of the rats the D lever was the left lever, for the other half it was the right lever Responding on the inappropriate lever had no programmed consequences The reinforced lever was alternated in each chamber during daily consecutive sessions. Daily 15 min-sessions were run from Monday to Friday Drug (D) or saline (S) sessions were given according to 2-weekly alternating sequences (1) S-D-D-S-S-D-S-S-D-D and (2) D-S-S-D-D-S-D-D-S-S Both experimental groups were divided into two subgroups. One subgroup started discrimination training with sequence (1), the other with sequence (2) During the initial four weeks of discrimination training, the FR schedule was gradually changed into a tandem variable interval 40 sec-fixed ratio 10 schedule (VI 40″-FR 10, after a mean of 40 sec ten responses were required to obtain the reinforcer) When this final schedule was in effect, control sessions were run on Tuesdays and Thursdays, one under D and one under S. During control sessions an extinction period was introduced at the beginning of the 15 min-session The extinction period ended 2 min after lever selection (i e , accumulation of 10 responses on one of the two levers) had occurred It yielded two measures (1) "percentage injection-appropriate lever responses," calculated as the number of responses on the injection-appropriate lever, divided by the total number of responses on both levers (×100), (2) "number of responses," calculated as the number of responses on both levers

Generalization Test Procedure

Generalization tests started when both groups showed highly accurate and stable discrimination performance (under both training conditions, mean % injection appropriate responses ≥90) Test sessions occurred on Wednesdays and Fridays, while training (including control sessions) continued on the remaining days On test days, rats were injected IP with a particular dose of a test drug For each dose, half of the tests followed a D session on the preceding day, the other half followed a S session After 15 min the animal was placed in its chamber and was allowed to respond during a time interval covering lever selection +2 min Test session ended after this interval or, in the case of insufficient responding, after 15 min No reinforcement could be obtained Testing yielded two measures (1) "percentage drug lever responses," calculated as the number of responses on the D lever divided by the total number of responses on both levers (×100), (2) "number of responses," calculated as the total number of responses on both levers Ten responses were required in order to take account of the first measure Both group CDP and group PB were tested with different doses of CDP, PB, Ro 15-1788 and CGS 8216, and the BDZ antagonist vehicle

Antagonism Test Procedure

Antagonism tests were essentially similar to the generalization tests Each rat was injected IP with the BDZ antagonist and 15 min later with a substitution dose of either CDP or PB Substitution doses of CDP and PB were chosen on the basis of their ability to substitute for the training drug condition in each experimental group (≥90% drug lever responses) Both experimental groups were tested with different doses of Ro 15-1788 + the substitution doses of CDP and PB, with the BDZ antagonist vehicle + the substitution doses of CDP and PB, and finally with different doses of CGS 8216 + the substitution doses of CDP and PB

Data Analyses

For each training condition (D and S), individual base-line values of discriminative responding were obtained by averaging the "percentage injection-appropriate responses" values obtained during the test phase of the experiment Base-line values, as well as generalization and antagonism test results were, after arc-sine transformations, analyzed by means of ANOVA [23]. Differential effects of test dose were analyzed by the Newman-Keuls method [23] Effects of test drug on "number of responses" were analyzed by means of Friedman two-way ANOVA and Wilcoxon test [11]

Drugs

CDP Hydrochloride (Hoffmann-La Roche, Basle, Switzerland) and Sodium PB (OPG, Utrecht, The Netherlands) were dissolved in 0 9% NaCl solution (saline) Ro 15-1788 (Hoffmann-La Roche, Basle, Switzerland) and CGS 8216 (Ciba-Geigy, Basle, Switzerland) were suspended in distilled

TABLE 1

GENERALIZATION TEST RESULTS OBTAINED WITH CDP AND PB IN TWO GROUPS OF RATS, TRAINED TO DISCRIMINATE EITHER 4 mg/kg CDP (LEFT PANEL), OR 10 mg/kg PB (RIGHT PANEL) FROM SALINE

Group CDP (N=8)				Group PB (N=8)			
Drug	Dose (mg/kg)	C	Mean % drug lever responses (S E.M.)	Drug	Dose (mg/kg)	C	Mean % drug lever responses (S E M.)
CDP	0 63	8	15.5 (10 5)	PB	1 25	8	3 8 (3 3)
	1 25	8	44.0 (13 4)		2 5	8	18 9 (11 8)
	2 5	8	75 5 (12 0)		5	8	59.5 (16.5)
	4 0	8	94 2 (1 7)		10	8	97 6 (0 8)
	5 0	8	94 8 (2 1)				
PB	2 5	8	36 9 (10.3)	CDP	1 25	8	2.9 (2 2)
	5	8	61.4 (12.5)		2 5	8	57 6 (12.0)
	10	8	90 4 (3 5)		5	8	69 9 (14 2)
					10	8	94.9 (2.1)

Column C shows the number of animals on which calculation of the generalization index was based (rats performing at least 10 responses during generalization tests).

water to which Tween 80 (2 drops/10 ml) was added (vehicle). All drugs were administered IP in an injection volume of 2 ml/kg. Doses of CDP and PB refer to the salts.

RESULTS

Drug Stimulus Control

All rats showed excellent drug-induced stimulus control when generalization tests started (after 100 training sessions) Mean base-line values (95% confidence limits) of discriminative responding under drug and saline respectively were· 97.3 (95.2–99.4)% and 98.0 (96.1–99.9)% for group PB; and 94 2 (88.1–100)% and 94.2 (89.7–98.7)% for group CDP There was no statistical evidence for a difference (or interaction) in discriminative responding between either the experimental groups, or the alternative training conditions. In both groups, one rat died during the test phase of the experiment. Results of these rats were, as far as possible, included in the different analyses

Generalization Tests CDP and PB

Test results obtained with CDP and PB are shown in Table 1 for each experimental group separately. Administration of the compounds resulted in dose-dependent generalization with the CDP and PB training drug conditions Because complete generalization was apparent in both groups, substitution doses of CDP and PB (doses which resulted in ≥90% drug lever responses) could be obtained 4 mg/kg CDP and 10 mg/kg PB for group CDP, and 10 mg/kg CDP and 10 mg/kg PB for group PB.

Generalization Tests· Ro 15-1788 and CGS 8216

Test results obtained with Ro 15-1788 are shown in Fig 1 (upper panel, group CDP) and Fig. 2 (upper panel, group PB). Administration of 0.31–20 mg/kg Ro 15-1788 resulted in dose-dependent generalization in CDP trained animals, $F(4,24)=5.97$, $p<0$ 005, but not in PB trained animals. Discriminative responding after administration of 5 and 20 mg/kg Ro 15-1788 to the CDP trained animals, significantly

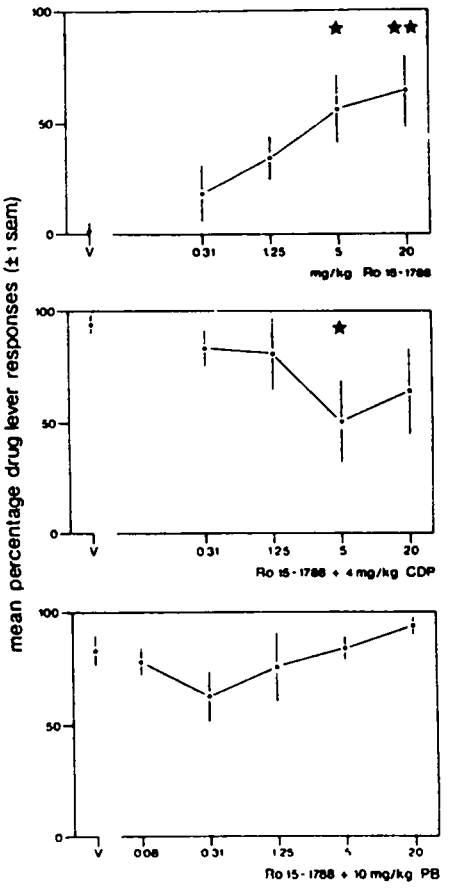

FIG 1 Generalization and antagonism test results obtained with Ro 15-1788 in rats, trained to discriminate CDP (4 mg/kg, IP) from saline Rats were tested with Ro 15-1788 (upper panel), Ro 15-1788 + CDP (4 mg/kg) (middle panel) and Ro 15-1788 + PB (10 mg/kg) (lower panel) Upper panel shows CDP like discriminative effects of Ro 15-1788 Points at "V" indicate the effects of the vehicle Asterisks indicate statistically significant differences with the vehicle condition (★$p<0$ 05, ★★$p<0.01$)

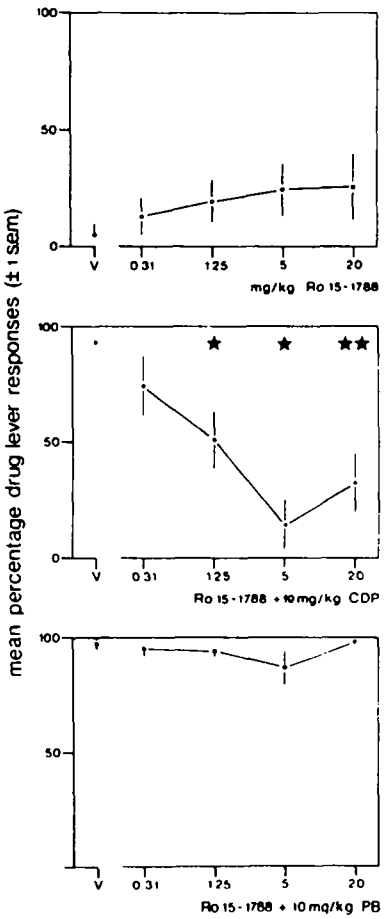

FIG 2 Generalization and antagonism test results obtained with Ro 15-1788 in rats, trained to discriminate PB (10 mg/kg, IP) from saline Rats were tested with Ro 15-1788 (upper panel), Ro 15-1788 + CDP (10 mg/kg, IP) (middle panel) and Ro 15-1788 + PB (10 mg/kg, IP) (lower panel) Points at "V" indicate the effects of the vehicle Asterisks indicate statistically significant differences with the vehicle condition (★$p<0$ 05,★★$p<0$ 01)

differed from the vehicle test condition ($q_4=4$ 47, $df=24$, $p<0.05$ and $q_5=6$ 40 $df=24$, $p<0$ 01, respectively)

Generalization test results obtained with CGS 8216 are shown in Table 2 (upper part) Some rats failed to totalize 10 responses during test sessions ANOVA including only the animals which responded under each test condition (column C), showed that CGS 8216 did not induce drug-appropriate responding in both experimental groups Higher doses of CGS 8216 were not tested because of the response rate decreasing effects

Antagonism Tests Ro 15-1788

Antagonism of a CDP substitution dose by Ro 15-1788 is shown in the middle panels of Fig 1 (group CDP) and Fig. 2 (group PB) Co-administration of 0 31–20 mg/kg Ro 15-1788 affected discriminative responding in the CDP trained animals, $F(4,20)=2,80$, $p=0.054$, as well as in the PB trained animals, $F(4,24)=9$ 92, $p<0.001$ Differential analysis showed a significant effect on CDP induced discriminative responding by 5 mg/kg Ro 15-1788 ($q_4=4$ 34, $df=20$, $p<0$ 05) in group CDP, and by 1 25 mg/kg ($q_3=4$ 08, $df=24$, $p<0$ 05), 5 mg/kg ($q_4=7$ 99, $df=24$, $p<0$ 01) and 20 mg/kg ($q_5=5$ 85, $df=24$, $p<0$ 01) Ro 15-1788 in group PB

Failure of antagonism of a PB substitution dose by Ro 15-1788 is shown in the lower panels of Fig 1 (group CDP) and Fig 2 (group PB) In both groups, there was no statistical evidence for an effect of Ro 15-1788 on PB induced discriminative responding These results show that, regardless of the experimental group, a dose range of Ro 15-1788 which successfully affected discriminative responding induced by CDP, had no effect on PB induced responding

Antagonism Tests CGS 8216

Antagonism of a CDP substitution dose by CGS 8216 is shown for each group in Table 2 (middle part) It was found that co-administration of CGS 8216 affected discriminative responding in the CDP trained rats, $F(2,10)=6$ 56, $p<0$ 025, as well as in the PB trained rats, $F(3,9)=6$ 55, $p<0$ 025 Significant effects on CDP induced discriminative responding were obtained with 10 mg/kg CGS 8216 ($q_3=5$ 08, $df=10$, $p<0$ 05) in group CDP, and with 10 mg/kg ($q_3=4$ 13, $df=9$, $p<0$ 05) and 20 mg/kg ($q_3=6$ 12, $df=9$, $p<0$ 01) CGS 8216 in group PB In both groups, there was no statistical evidence for an effect of CGS 8216 on PB induced discriminative responding (Table 2, lower part) Higher doses of CGS 8216 were not tested because of response rate decreasing effects These results show that, just like Ro 15-1788, regardless of the experimental group, a dose range of CGS 8216 which successfully affected discriminative responding induced by CDP, had no effect on PB induced responding

Response Rate

Median base-line number of responses (95% confidence limits) obtained under the drug and saline training conditions respectively were 138 (110–231) and 93 (64–200) for group PB, and 239 (199–289) and 166 (108–199) for group CDP Except for a response rate increasing effect observed after administration of the training drug condition in group CDP (4 mg/kg CDP, T=0, N=8, $p<0$ 01), generalization tests with CDP and PB had no effect on response rate in either group (data not shown) Median number of responses obtained with Ro 15-1788 (administered alone or in combination with CDP or PB) ranged from 39 (15–169) (5 mg/kg Ro 15-1788 + 10 mg/kg CDP, group PB) to 176 (94–298) (1 25 mg/kg Ro 15-1788 + 10 mg/kg PB, group PB) In general, no statistical evidence was obtained for response rate modulating effects of Ro 15-1788 However, when administered in combination with 4 mg/kg CDP (group CDP), Ro 15-1788 significantly affected response rate ($\chi^2_r=13$ 94, $df=4$, $p<0$ 01), suggesting that the response rate increasing effects of CDP (Vehicle + 4 mg/kg CDP 294 (288–395)) were counteracted by co-administration of Ro 15-1788 Median response rate data obtained with CGS 8216 ranged from 2 (0–185) (10 mg/kg CGS 8216, group CDP) to 138 (75–420) (2 5 mg/kg CGS 8216 + 10 mg/kg PB, group PB) In both groups, a dose-dependent decrease in response rate generally was observed with CGS 8216, administered either alone, or in combination with CDP or PB (χ^2_r ranging from 6 33 ($df=2$, $p<0$ 05, 2 5–10 mg/kg CGS 8216 + 10 mg/kg PB, group CDP) to 16 26 ($df=3$, $p<0$ 01, 2 5–20 mg/kg CGS 8216 + 10 mg/kg CDP group PB)) Taken together, these results indicate that similar dose ranges of both antagonists differentially affected response rate

TABLE 2

GENERALIZATION AND ANTAGONISM TEST RESULTS OBTAINED WITH BENZODIAZEPINE ANTAGONIST CGS 8216 IN TWO GROUPS OF RATS, TRAINED TO DISCRIMINATE EITHER 4 mg/kg CDP (LEFT PANEL), OR 10 mg/kg PB (RIGHT PANEL) FROM SALINE

Group CDP (N=7)				Group PB (N=7)			
Treatment 1 (t-30 min) Drug (Dose in mg/kg)	Treatment 2 (t-15 min) Drug (Dose in mg/kg)	C	Mean % drug lever responses (S E M)	Treatment 1 (t-30 min) Drug (Dose in mg/kg)	Treatment 2 (t-15 min) Drug (Dose in mg/kg)	C	Mean % drug lever responses (S E M)
—	vehicle	7	1 6 (0 9)	—	vehicle	7	5 7 (5 2)
—	CGS 8216 (2 5)	7	15 3 (11 2)	—	CGS 8216 (2 5)	7	2.4 (2.0)
—	CGS 8216 (10)	2	0 0 (0 0)	—	CGS 8216 (10)	6	1 3 (0.9)
				—	CGS 8216 (20)	6	0 0 (0 0)
vehicle	CDP (4)	7	93 7 (4 3)	vehicle	CDP (10)	7	93 3 (2.3)
CGS 8216 (2 5)	CDP (4)	7	81 5 (10 7)	CGS 8216 (2 5)	CDP (10)	6	72 8 (10 7)
CGS 8216 (10)	CDP (4)	6	43 5 (14 8)*	CGS 8216 (10)	CDP (10)	4	24 0 (17 2)*
				CGS 8216 (20)	CDP (10)	4	11 6 (10 6)†
vehicle	PB (10)	7	82 7 (6 6)	vehicle	PB (10)	7	96 6 (1 9)
CGS 8216 (2 5)	PB (10)	7	74 4 (7 6)	CGS 8216 (2 5)	PB (10)	7	84 3 (13 3)
CGS 8216 (10)	PB (10)	5	73 8 (10 4)	CGS 8216 (10)	PB (10)	6	77 2 (15 6)
				CGS 8216 (20)	PB (10)	7	84 4 (14 1)

Column C represents the number of animals on which calculation of the index was based *Significantly different from vehicle + CDP, $p<0.05$ †Significantly different from vehicle + CDP, $p<0.01$

DISCUSSION

Research on the DS properties of BDZs and barbiturates has shown that these compounds may substitute for each other in rats trained to discriminate either compound from vehicle (e g , [2,15]) In particular, it has been shown that mutual substitution between CDP and PB, as obtained in a two-lever food-reinforced discrimination procedure, was independent of the training dose level (De Vry and Slangen, unpublished results). In accordance with these findings, it was found in the initial part of the present study that CDP and PB dose-dependently substitute for each other. This result strongly suggests that the DS of CDP and PB share qualitatively closely similar properties when assessed under the present experimental conditions. However, it does not necessarily implicate that the DS properties of CDP and PB are mediated by similar mechanisms of action In the subsequent part of the study we therefore explored the possibility of using BDZ receptor antagonists as a method for differentiating between the discriminative effects of CDP and PB

Thus far, selective effects of Ro 15-1788, a proposed BDZ receptor antagonist [12], on discriminative responding induced by PB and the BDZ compound diazepam have been reported in a shock avoidance procedure [11] Similarly, it has been shown that discriminative effects of CDP and diazepam, but not of the barbiturates PB and barbital, were affected by co-administration of Ro 15-1788 in rats, trained to discriminate PB from saline in a milk-reinforced operant task [24]. Ro 15-1788 also was found to selectively reverse antagonism of the pentylenetetrazol stimulus by the BDZs diazepam and des-methylclobazam, but not by PB [8]. Another proposed BDZ receptor antagonist, CGS 8216 [3] was found to block the discriminative effects of diazepam, but not those of PB, in rats discriminating the effects of PB or diazepam in a shock avoidance procedure [14,20]

In the present study, a differential effect of both Ro 15-1788 and CGS 8216 on discriminative effects of CDP and PB was found in CDP trained rats, as well as in PB trained rats. The present results therefore extend previously obtained findings to a situation where selectivity of both antagonists could be assessed in subjects similarly trained to discriminate the effects of either a BDZ or a barbiturate in a food-reinforced two-lever procedure.

The differential effects of both BDZ antagonists on discriminative responding induced by BDZs and barbiturates found in various procedures, suggest different mechanisms of action for the discriminative effects of BDZs and barbiturates. It has been proposed that Ro 15-1788 and CGS 8216 are valuable tools to demonstrate involvement of BDZ receptors in the behavioral effects of a compound [9,22]. Differential effects of both antagonists on CDP and PB induced discriminative responding therefore suggest that the discriminative effects of CDP, but not those of PB, may result from interaction with BDZ receptors. The similarity between the DS properties of CDP and PB could be related to the observation that BDZ binding sites may be part of a macromolecular protein complex which additionally contains GABA binding sites with associated chloride ionophores and binding sites for barbiturates and picrotoxin [17] It may thus be possible that, although different mechanisms of action seem to be involved, the discriminative effects of CDP and PB, at least partly, are subserved ultimately by the same macromolecular protein complex. However, as the exact nature of the DS properties of BDZs and barbiturates remains to be elucidated, additional differences between the mechanisms of action mediating their discriminative effects, cannot be ruled out.

Although Ro 15-1788 and CGS 8216 both have selective effects on CDP and PB induced discriminative responding, several findings suggest differences in the mechanism of action of the two BDZ antagonists. First, Ro 15-1788 (5 and 20 mg/kg) significantly induced CDP like responding, whereas no such effect was obtained with CGS 8216. Similarly, some rats responded exclusively on the PB associated lever when

injected with 5 and 20 mg/kg Ro 15-1788; a finding not observed after administration of CGS 8216. These results may suggest that administration of Ro 15-1788 may result in discriminative effects, which are (at least partly) similar to the DS properties of CDP and PB. Accordingly, it has recently been shown that 10 mg/kg Ro 15-1788 may induce drug stimulus control in the rat [5] and preliminary results suggest that both CDP and PB significantly generalize to the Ro 15-1788 training condition It is interesting to note that partial generalization of Ro 15-1788 to the CDP training condition was observed in addition to partial antagonism of the CDP stimulus by the same dose range of Ro 15-1788 One other drug discrimination study reports considerable BDZ like effects of Ro 15-1788 (40–80 mg/kg, IP) in chlorazepate trained animals, whereas Ro 15-1788 was found unable to antagonize the discriminative effects of chlorazepate [4] Moreover, it has been shown that both the extent of generalization of Ro 15-1788 to the CDP training condition, and the extent of antagonism of the CDP training condition by Ro 15-1788, are determined by the CDP training dose [6] These results therefore suggest that Ro 15-1788, contrary to CGS 8216, has mixed BDZ like agonist-antagonist behavioral effects in the drug discrimination procedure

Second, Ro 15-1788 and CGS 8216, either administered alone or in combination with CDP or PB, had different effects on response rate (number of responses emitted during extinction tests). Ro 15-1788 had no effect on response rate, except for the condition in which it was co-administered with 4 mg/kg CDP (group CDP) In the latter case it may be suggested that the response rate increasing effects induced by CDP were counteracted by Ro 15-1788. CGS 8216, on the other hand, severely depressed response rate in all test conditions This general depressing effect also was reflected in the number of non-responding animals Dose-dependent decreases in response rate similarly were reported in rats trained with diazepam and tested with CGS 8216 or CGS 8216 + diazepam [19]

It may be hypothesized that the behavioral differences between Ro 15-1788 and CGS 8216, reflect differential interactions of both compounds with the macromolecular protein complex, containing BDZ binding sites, GABA binding sites and chloride ionophores [17] Both antagonists selectively bind to BDZ receptors, and initially were characterized as BDZ antagonists without BDZ like effects at the effective antagonist dose range [3, 10, 12] Subsequently however, Ro 15-1788 occasionally has been characterized as a partial BDZ agonist, whereas CGS 8216 because of its effects opposite to the effects of classical BDZs, has been characterized as a weak "inverse" BDZ agonist (e g , [7, 13, 16]) The behavioral effects of Ro 15-1788 in this study support its characterization as a partial agonist, however it is presently unclear to what extent "inverse agonist" properties of CGS 8216 may have contributed to its behavioral effects in the drug discrimination procedure

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