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Discriminative Stimulus Properties of RU 33965, a Benzodiazepine Receptor Weak Partial Inverse Agonist

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GARDNER, C. R., P. BUDHRAM AND F. L. PARKER. *Discriminative stimulus properties of RU 33965, a benzodiazepine receptor weak partial inverse agonist.* PHARMACOL BIOCHEM BEHAV 43(2) 583–588, 1992.—Rats were trained to discriminate the low-efficacy benzodiazepine receptor inverse agonist RU 33965 from vehicle in a two-lever discrimination task on a fixed ratio (FR) 20 schedule. Consistent discrimination was obtained at 0.5 mg/kg PO RU 33965. Both leptazol and stronger inverse agonists (FG7142, S-135, RU 34000) substituted for the cue. The weak inverse agonists/antagonists RU 33094, RU 34030, Ro 15-1788, and ZK 93426 also substituted for the cue with the latter two compounds being particularly potent. The agonist and partial agonists diazepam, RU 33203, and RU 39419 did not substitute for the RU 33965 cue but RU 39419 antagonised it. The full agonists diazepam and loprazolam only consistently antagonised the cue when given IP 5 min pretest. These data suggest that the RU 33965 cue results from its weak inverse agonist activity at benzodiazepine receptors, but kinetic factors must be considered when interpreting drug effects in discrimination studies.

Drug discrimination RU 33965 Benzodiazepine receptors Rats

DRUG discrimination studies have played a valuable role in the investigation of the functions of $GABA_A$/benzodiazepine receptors. The ability of benzodiazepine receptor ligands to either antagonise or substitute for the leptazol cue has allowed assessment of the efficacies of these ligands. The benzodiazepine receptor remains unique in showing bidirectional efficacy of ligands, with agonists possessing positive efficacy (enhancement of GABA responses) and inverse agonists possessing negative efficacy (reduction of GABA responses). Both types of ligand are blocked by antagonists. Both partial agonists and partial inverse agonists have been discovered, leading to the suggestion that there is a bidirectional agonist-antagonist-inverse agonist functional continuum (1,11,18,25). Cues induced by classical benzodiazepine agonists such as diazepam or chlordiazepoxide extended the ability to characterise the efficacies of ligands, particularly agonists. The use of lower training doses of these drugs (5) or the use of partial agonists as training drugs (1,9) enhanced the resolution of small differences in partial agonist efficacies or functional effects. Low-efficacy partial agonists may substitute for a cue induced by another partial agonist but antagonise a cue induced by a full agonist. It has been possible to train rats to discriminate compounds with very weak agonist efficacies (e.g., CGS 9896 and CGS 9895) from their vehicle (2).

Drug discrimination studies have helped identify different functional correlates of activation of BDZ_1 and BDZ_2 receptor subtypes with BDZ_1-selective agonist or partial agonist ligands CL 218872 and zolpidem having been successfully used as training drugs (8,22). The use of some β-carboline partial agonists as training drugs (e.g., ZK 95962) has produced some inconsistent results that may lead to a more detailed understanding of functional correlates of benzodiazepine receptor subtypes (1).

Discriminative stimuli appear to be useful in detecting small differences in efficacies of ligands for specific receptors, such as partial agonism of 5-hydroxytryptamine$_2$ (5-HT_2) receptor antagonists (14). Other pharmacological methods may be less sensitive to such differences in efficacy or may require a battery of tests. As with partial agonists, it would be useful to develop partial inverse agonist cues to detect weak efficacy. The benzodiazepine receptor antagonist Ro 15-1788 (flumazenil) appears to possess weak efficacy under certain circumstances (6) and has also been successfully used as a training drug, but the discriminative stimuli induced do not predict one specific level of efficacy of benzodiazepine receptor activation. Both agonists and some inverse agonists, as well as leptazol, will substitute for this cue (26).

The full-inverse agonist DMCM and the partial inverse agonist FG 7142 have both been used as training drugs (19–21), but the risks of kindled seizures and depression of operant performance by these drugs present problems to their use. The discriminative stimulus properties of FG 7142 have been

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associated with its anxiogenic properties (19,20). Low-efficacy partial inverse agonists may have therapeutic potential in enhancing cognitive processes (23). There are kinetic problems with the low-efficacy inverse agonist CGS 8216 (17) and at present there is no reliable discriminative stimulus induced by a compound with such weak efficacy.

A series of 3-cyclopropyl carbonyl imidazobenzodiazepines has recently been developed that have good absorption characteristics and are not rapidly metabolised to inactive molecules (3,4,10,15,24). Several of these molecules possess very low inverse agonist efficacy. In particular, RU 33965 has been well characterised pharmacologically. RU 33965 was not convulsive in rodents but did potentiate leptazol seizures in mice. This potentiation never reached 100% and was antagonised by flumazenil (4). At the ED_{50} dose for potentiation of seizures, RU 33965 occupied virtually all in vivo benzodiazepine binding sites in comparison with an occupancy of only 9% by DMCM (4,10). These data suggest that RU 33965 possesses only weak inverse agonist efficacy. Other pharmacological studies are consistent with this hypothesis. RU 33965 was relatively weak and inconsistent in reducing GABA-mediated synaptic inhibition in cerebellar slices (24). This compound was potent in antagonising a chlordiazepoxide cue but only substituted for a leptazol cue at very high doses. Similarly, RU 33965 was potent in blocking a classical benzodiazepine in the suprahyoid muscle twitch model in urethane-anaesthetised rats but only induced twitch itself at very high doses (4). As suggested for other low-efficacy inverse agonists, RU 33965 may enhance learning and memory processes (3). In particular, both RU 33965 and its close analogue RU 34030, tested here, reversed an atropine-induced deficit in learning in the Morris water maze (15).

The combination of low inverse agonist efficacy and good absorption with metabolic stability suggested that RU 33965 would make an ideal training drug to detect such low inverse agonist efficacy at benzodiazepine receptors. Initial studies indicated that rats could easily be trained to discriminate RU 33965 from vehicle and therefore the pharmacological characteristics of this cue have been investigated.

METHOD

Subjects

Male hooded Lister rats (Olac, Bicester, UK) were used in all these studies. At the beginning of training, rats were 180–220 g and spent their working lives performing these experiments as long as their baseline responding was stable. Therefore, most pharmacological studies were performed with rats weighing 300–550 g.

Animals were housed in pairs in a colony room maintained at 22°C and with controlled humidity, on an 0800–1800, 1800–0800 h light–dark cycle. Water was continuously available in the home cages, but food was restricted to 80% of that consumed by ad lib fed controls. Rats were fed approximately 4 h after the operant session. Eight rats were used for discrimination training with RU 33965. Each member of a pair was trained on the same cue drug, and both were tested in different operant chambers but at the same time.

Apparatus

The behavioural apparatus consisted of identical standard Skinner boxes (Camden Instruments, London, UK) each with two retractable levers on one wall, with the food dispensing magazine centrally between them. Each apparatus was housed in a light-proof, sound-attenuated, fan-ventilated chamber.

Operation of the behavior schedules and recording of data were achieved using microcomputers (Acorn Series II) via appropriate interfacing (Camden Instruments). Levers were retracted when rats were placed in the apparatus and each session began when both levers were simultaneously presented.

Discrimination Training

Rats were trained to discriminate between the effect of vehicle and that of RU 33965 (2 mg/kg, PO, 1 h prior to the test). When rats were fully trained and a dose-response curve had been obtained, the training dose was reduced to 0.5 mg/kg PO and stable responding reestablished prior to pharmacological studies.

Rats were magazine trained and shaped to press the lever for food presentation (45-mg pellets, Camden Instruments) with only one lever present. Then they were trained to respond on one of two levers following cue drug injection and on the other lever following administration of vehicle (demineralised water, 2 ml/kg). A food pellet was delivered after every 20th press [fixed ratio (FR) 20] on the correct lever. Responses on the incorrect lever (i.e., drug lever after vehicle injection or vehicle lever after cue drug injection) were recorded but were not reinforced with food pellet reward.

The drug lever was randomly allocated on the right side of the food magazine for half the rats and on the left side for the other half. The position of the drug and vehicle levers remained constant for each rat for all subsequent sessions. The sequence of drug vehicle injection was different throughout groups of rats to control for a possible olfactory cue and a quasirandom (vehicle–drug–drug–vehicle–vehicle and drug–vehicle–vehicle–drug–drug) sequence of testing was used for each successive two-week, Monday-to-Friday test block.

Training criterion was reached when the number of presses prior to receiving the first food pellet (FFP) was <24 for the prior two sessions of both drug and vehicle training. This criterion was maintained throughout drug testing as an index of stable baseline responding. In the majority of cases, the FFP was 20 under these fully trained conditions.

Drug Testing

Rats reaching the criterion level of performance were repeatedly used in generalisation and antagonism testing. At least one vehicle and one cue drug response at criterion level was required between each such test. Any given drug/dose combination was allocated randomly to rats as they became available for testing. When necessary, the route of vehicle administration was changed if a test compound in generalisation studies was to be given by a different route or at a different pretest time from the cue drug. In antagonism studies, when both test compound and cue drug were given an appropriate vehicle injection was given as well as the cue drug in control tests. Vehicle and cue drug test sessions were 10 min in duration, while tests with noncue drugs were 5 min in duration. Following the choice in the test sessions, reward was available on an FR 20 schedule on the lever of choice.

Drugs

All drugs were dissolved or suspended in appropriate vehicle (demineralised water for oral injections, 2 ml/kg and 0.9% saline for IP or SC injection, 1 ml/kg), sonicated, and continuously stirred until used.

We acknowledge the generous gifts of flumazenil and Ro 14-7437 from Hoffman La Roche, Basle, Switzerland. Diazepam, FG7142, and leptazol were obtained commercially and all other compounds tested were synthesised by chemists from Roussel Laboratories (Paris, France).

RESULTS

Following 23 training sessions dosed with either vehicle or 2 mg/kg PO RU 33965, with reinforcement only available following responses on a single lever, rats were entered into the quasirandom testing sequence with responses on both levers reinforced. Rats responded at criterion level for an established discriminative stimulus either immediately or within six sessions. Other pharmacological evidence obtained in parallel experiments suggested that RU 33965 could antagonise benzodiazepine agonists at lower doses than the training dose and that it may occupy virtually all benzodiazepine receptors at this dose as measured by in vivo benzodiazepine receptor binding (4). Following establishing a dose-response curve for RU 33965 to induce discrimination, the training dose was reduced to 0.5 mg/kg PO and criterion discrimination responding reestablished. In three rats, criterion was reached immediately and the remaining rats reached criterion within 11 sessions. When all rats were responding at criterion, another dose-response curve for RU 33965 was established. RU 33965 was more potent in inducing a discriminative stimulus when rats were fully trained on the lower training dose (Fig. 1).

These rats were then used routinely for pharmacological studies. Three compounds known to be benzodiazepine receptor inverse agonists—S-135, FG7142, and RU 34000 (7)—substituted for the RU 33965 cue in a dose-related manner. Similarly, leptazol substituted for the RU 33965 cue (Fig. 2). Although compounds are routinely given orally 1 h pretest, FG 7142 and leptazol were administered via routes (IP and SC, respectively) and retest times (30 and 15 min, respectively) that are known to optimise their pharmacological effect in vivo.

Four benzodiazepine antagonists or very-low-efficacy inverse agonists:—flumazenil, ZK 93426, RU 33094, and RU 34030—also substituted for the RU 33965 discriminative cue. Dose-response curves tended to be irregular, particularly with ZK 93426 (Fig. 3). Flumazenil (Ro 15-1788, given IP 30 min pretest) showed 67% or more substitution at 1,2,5,10, and 20 mg/kg but only 33% substitution at 0.1 and 0.2 mg/kg. RU 34030, the 8 fluoro analogue of RU 33965, was most potent in substituting for the RU 33965 cue, showing 83% or more substitution at 0.5, 1, and 2 mg/kg PO and 50% substitution at 0.05, 0.1, and 0.2 mg/kg PO (Fig. 3). A single dose of

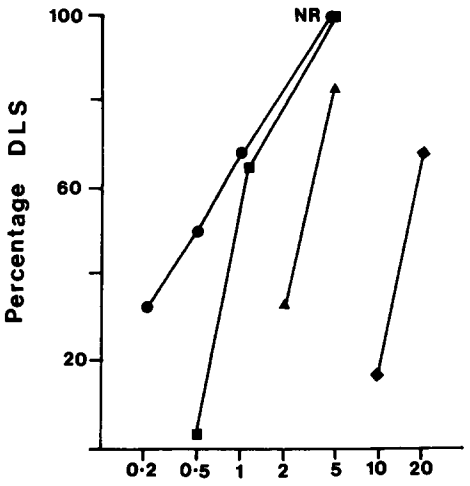

FIG. 2. Ability of some benzodiazepine receptor inverse agonists and leptazol to substitute for the RU 33965 cue. Doses in mg/kg are shown below the axis. S-135 (●-●) and RU 34000 (■-■) were administered orally 1 h pretest, FG 7142 (▲-▲) was given IP 30 min pretest, and leptazol (♦-♦) was given SC 15 min pretest. The percentage of rats showing drug-lever selection (DLS) is shown. All dose levels were tested in six rats. NR, rats not responding to criterion on test.

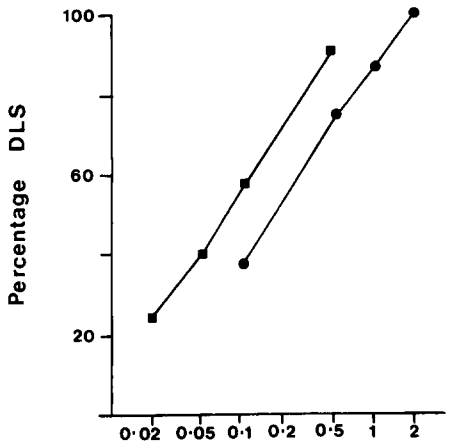

FIG. 1. Dose-response curves for RU 33965 in substituting for the discriminative stimulus induced by RU 33965 2mg/kg PO (●-●) and in the same rats after retraining with RU 33965 at 0.5 mg/kg PO (■-■). Data are shown as the percentage of rats tested that selected the drug lever (% DLS). Doses are shown below the axis in mg/kg PO and the drug was given 1 h prior to testing. Each dose level was tested in 8–15 rats except 0.02 mg/kg, which was tested in 4 rats.

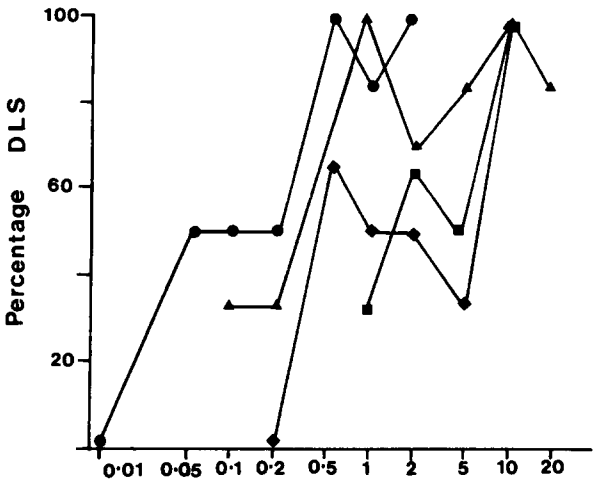

FIG. 3. Ability of some benzodiazepine antagonists or low-efficacy inverse agonists to substitute for the RU 33965 cue. Doses in mg/kg are shown below the axis. Ro 15-1788(▲-▲) was given IP 30 min pretest, RU 34030 (●-●) an RU 33094 (■-■) were given PO 1 h pretest, and ZK 93426 (♦-♦) was given PO 30 min pretest. The percentage of rats showing drug-lever selection (DLS) is shown. All dose levels were tested in six rats.

TABLE 1

STIMULUS GENERALISATION AND ANTAGONISM USING RATS DISCRIMINATING RU 33965 FROM VEHICLE

Drug	Dose (mg/kg)	Route	Pretreatment Time	Rats Selecting Drug Lever	
				No.	%
Ro 14-7437	1	IP	30 min	4/6	66.7
RU 39419	20	PO	1 h	1/6	16.7
RU 33203	10	PO	1 h	0/5	0
Diazepam	2	PO	1 h	1/6	16.7
	5	PO	1 h	2/6	33.3
Cue + Diazepam	2	PO	1 h	3/6	50
	5	PO	1 h	4/6	66.7
	10	PO	1 h	5/6	83.3
	5	IP	5 min	3/6 NR	50
	7.5	IP	5 min	1/3	33.3
Cue + Loprazolam	2	IP	1h	2/6	33.3

NR, rat not responding to criterion on test.

Ro 14-7437 (1 mg/kg IP 30 min pretest) was tested and this benzodiazepine antagonist also showed partial substitution for the RU 33965 cue (Table 1).

Diazepam and two partial agonists RU 39419 and RU 33203, all given PO at doses that show marked substitution for a chlordiazepoxide cue and antagonism of a leptazol cue in our laboratories, did not show any marked substitution for the RU 33965 cue (Table 1). When given orally in combination with the cue drug, RU 39419 clearly antagonised the RU 33965 cue (Fig. 4) at 2,5,10, and 20 mg/kg, but diazepam did not show marked or dose-related inhibition of the cue (Table 1).

Further investigation of the interaction between classical benzodiazepines and the RU 33965 cue showed that, given IP 1 h prior to test, loprazolam at a high dose (2 mg/kg) appeared to partially antagonise the cue (Table 1). However, when administered IP 5 min prior to testing loprazolam clearly inhibited the cue in a dose-related manner although not fully (Fig. 4), and the highest tolerated doses of diazepam also partially antagonised the cue (Table 1).

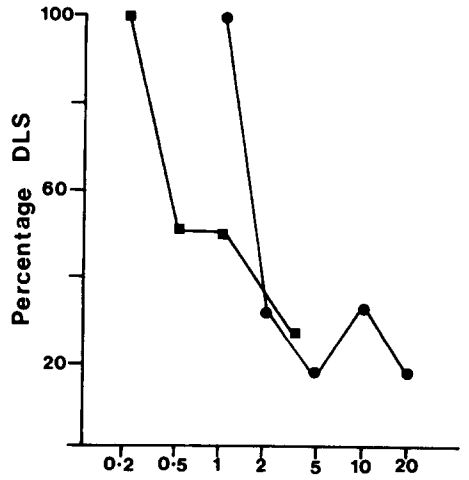

FIG. 4. Antagonism of the RU 33965 cue by RU 39419 (●-●) given PO 1 h pretest or loprazolam (■-■) given IP 5 min pretest. Doses in mg/kg are shown below the axis. Data are presented as the percentage of rats showing drug-lever selection (DLS) when the test compounds were administered, as well as the cue drug. All dose levels were tested in four to six rats.

DISCUSSION

The cue dose of RU 33965 was reduced during training primarily due to parallel observations showing near maximal occupancy of benzodiazepine binding sites in vivo at the original cue dose of 2 mg/kg PO (4). Having retrained rats at 0.5 mg/kg PO, they could detect lower doses of RU 33965 when a dose-response curve was constructed. This observation represents an example of increased sensitivity on stimulus fading that has been observed with several other discriminative stimuli (1,25).

The established RU 33965 cue was reliably discriminated by the colony of rats, allowing pharmacological studies. Benzodiazepine receptor inverse agonists established to possess stronger efficacy in a range of pharmacological models—FG7142, S-135 (6,7), and RU 34000 (7,11,12)—substituted for the RU 33965 cue. In the case of the latter two compounds, where full dose-response curves were constructed, substitution was complete. Leptazol also substituted for RU 33965. Leptazol substitutes for cues induced by other inverse agonists and inverse agonists substitute for discriminative stimuli induced by leptazol (1,6,7,19,25). However, four agents that possess only marginal inverse agonist efficacy or are benzodiazepine antagonists—RU 33094 (7,11,12), ZK93426, Ro 15-1788 (6,7), and RU 34030, a close analogue of RU 33965 (15)—also potently substituted for the RU 33965 cue. Dose-response curves were a little irregular in comparison with the curves for inverse agonists with stronger efficacy. This variability may result in part from low efficacy of the compounds resulting in less consistent discrimination. It is less likely that the use of different groups of rats for each dose was a major contributing factor, as the curves for stronger inverse agonists were more regular. However, in combination with low efficacy this experimental design may emphasise the variation in responses. Also, in cases where molecules are inactivated by

hydrolysis of ester groups (Ro 15-1788 and ZK 93426) kinetic variation at lower doses may contribute, particularly with ZK 93426 in these experiments, as it was administered orally.

These data suggest that this RU 33965 cue may detect compounds with very low benzodiazepine receptor inverse agonist efficacy. Doses of Ro 15-1788 and ZK 93426 detected in these tests are relatively low (7), but those of other substituting compounds are not strikingly lower than effective doses in other pharmacological tests, including drug discrimination studies in this strain of rats (6,7,11,15). This suggests that factors other than efficacy at benzodiazepine receptors may also influence the sensitivity of the RU 33965 cue. It is difficult to confirm that this cue results from an interaction of RU 33965 with central benzodiazepine receptors using blockade with a specific antagonist as the criterion. Ro 14-7437 is a close analogue of Ro 15-1788 and has been claimed to be a benzodiazepine receptor antagonist (16). A single test dose of Ro-14-7437 also substituted for RU 33965, precluding its use as an antagonist in these studies.

The benzodiazepine full agonist diazepam and the moderate or weak efficacy partial agonists RU 33203 and RU 39419, respectively (13), did not substitute for the RU 33965 cue at relatively high doses in comparison with their ability to antagonise a leptazol cue or substitute for chlordiazepoxide in this strain of rats in our laboratories (6,7,9,11). Thus, in contrast to the discriminative stimulus properties of Ro-15-1788 (5,26) substitution for the RU 33965 cue is unidirectional in terms of benzodiazepine receptor efficacy, with only antagonists or inverse agonists substituting. The sensitivity of the cue to compounds generally regarded as antagonists either implies great sensitivity to marginal, inverse agonist efficacy that they may possess (6,7) or that the antagonist "set point" of the benzodiazepine receptor functional continuum has been altered by repeated administration of RU 33965 (6).

The partial agonist with very weak efficacy, RU 39419 (13), clearly antagonised the RU 33965 cue although total antagonism was not obtained. This is consistent with the hypothesis that this cue is mediated via an interaction with benzodiazepine receptors. However, when given 1 h prior to testing, either PO or IP, the benzodiazepine full agonists diazepam and loprazolam showed weak and inconsistent antagonisms of the RU 33965 cue. Both compounds were more effective and consistent when administered IP 5 min pretest. It appears that the effect of these full agonists is related to the rising phases of their absorption, which may be more rapid.

This need not imply that different receptor types are involved. These data may be explained on the basis of competitive receptor occupancy. When given alone, full agonists have pharmacological effects at low receptor occupancies (6,7,13), whereas the cue dose of RU 33965 may occupy a large percentage of benzodiazepine receptors (4). Therefore, administration conditions for the full agonists would have to be optimised to achieve sufficient displacement of RU 33965 from the receptors to inhibit the discriminative stimulus it induces. RU 39419 has low efficacy at benzodiazepine receptors and is well absorbed in rats (13). Doses inducing pharmacological effects also occupy a large percentage of benzodiazepine receptors. It is, therefore, able to displace RU 33965 and antagonise its discriminative stimulus when administered by the usual dosing regime.

It is therefore concluded that the RU 33965 cue results from the weak inverse agonists properties of the compound at benzodiazepine receptors. However, the association of the cue with different phases of the absorption of the training drug, as well as the association of the effects of drugs (either substituting for or antagonising the cue) with different phases of their absorption, may be important factors influencing pharmacological profiles in drug discrimination studies.

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