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Stimulus properties of the "atypical" antipsychotic zotepine in rats: comparisons with clozapine and quetiapine

Andrew J. Goudie*, Judith A. Smith, Jon C. Cole

Psychology Department, Liverpool University, Eleanor Rathbone Building, Bedford Street North, Liverpool, L69 7ZA, UK

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Abstract

The stimulus properties of the "atypical" antipsychotic zotepine were assessed in three studies in rats. In Study 1, the ability of zotepine to generalise to clozapine was studied. Two groups of rats were trained to discriminate clozapine at 2 and 5 mg/kg. Clozapine induced full generalisation in both groups, with the generalisation curves shifted significantly to the left in the low dose group. In generalisation tests clozapine did not suppress responding. Zotepine induced dose-related generalisation in both groups, with full generalisation in the low dose group and 50% maximal generalisation in the high dose group at the highest dose that could be tested. In contrast to clozapine, zotepine induced substantial (50% or more) substitution for clozapine only at doses which suppressed responding. In Study 2 zotepine was investigated in rats trained to discriminate quetiapine (10 mg/kg). Quetiapine induced full generalisation and zotepine only induced 54% generalisation at the highest dose that could be tested. Generalisation was accompanied by response suppression induced by both quetiapine and zotepine. In Study 3 an attempt was made to train a zotepine discrimination (1 mg/kg increased to 2 mg/kg). Even after 150 training sessions it proved impossible to obtain reliable discriminative responding with zotepine. These data suggest that: (i) The actions of zotepine in discrimination assays are similar to, but not identical with, those of clozapine and quetiapine; (ii) The differences among the actions of clozapine, quetiapine and zotepine may be related to either the unique ability of zotepine to block noradrenaline (NA) uptake, or to its more marked affinity for D_2 receptors; (iii) The finding that zotepine only mimicked quetiapine up to a level of 54% was unexpected, since quetiapine and clozapine generalise reciprocally and zotepine generalised fully to (low dose) clozapine. This finding may also be related either to zotepine's ability to inhibit NA uptake or its relatively high D_2 affinity; (iv) Although zotepine clearly possesses discriminative properties, it is not possible to train it as a reliable stimulus, in contrast to clozapine and quetiapine. This may be due to its more marked D_2 receptor affinity. Collectively, these data demonstrate both similarities and differences between zotepine and other novel atypical antipsychotics in drug discrimination assays.

Keywords: Atypical antipsychotics; Zotepine; Clozapine; Quetiapine; Drug discrimination; Behaviour; Rats

1. Introduction

Zotepine is a clozapine congener considered to be an "atypical" antipsychotic with limited ability to induce extrapyramidal side effects (EPS) (Cooper et al., 2000; Kasper et al., 2001), probably because it induces low levels of striatal D_2 receptor occupancy at clinically effective doses (Barnas et al., 2001). Like clozapine, zotepine has efficacy against both positive and negative symptoms (Kasper et al., 2001; Petit et al., 1996). It can, like clozapine, also ameliorate cognitive dysfunction in schizophrenics (Meyer-Lindenberg et al., 1997). Zotepine also resembles clozapine in inducing weight gain and hyperlipidemia as a side effect (Wetterling, 2002; Wetterling and Mussigbrodt, 1999). In preclinical studies, zotepine resembles clozapine in a number of ways. In rodents, both drugs block behavioural effects of the *N*-methyl-D-aspartate (NMDA) antagonists dizocilpine and PCP (Bakshi et al., 1994; Gattaz et al., 1994; Corbett et al., 1995). Furthermore, Needham et al. (1996) reported that zotepine also resembles clozapine in other preclinical assays considered indicative of antipsychotic action, including antagonism of apomorphine-induced climbing and amphetamine-induced hyperlocomotion. Zotepine and clozapine only induce catalepsy in rats at doses

* Corresponding author. Tel.: +44-151-794-1124; fax: +44-151-794-2945.
E-mail address: ajg@liverpool.ac.uk (A.J. Goudie).

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considerably greater than those which inhibit amphetamine-induced hyperlocomotion (Needham et al., 1996). Such findings agree with clinical evidence that these two drugs do not induce marked EPS at therapeutic doses. Zotepine also resembles clozapine in protecting against cortical neurotoxicity induced by NMDA antagonists (Okamura et al., 2003), and in elevating cortical DA levels, an effect thought to be involved in the drugs' actions against negative symptoms and cognitive defects in schizophrenia (Rowley et al., 2000).

In vitro binding studies with animal and human brain tissue show that both zotepine and clozapine exhibit "polyvalent" pharmacology with affinity for many receptors (Needham et al., 1996; Richelson and Souder, 2000). These data are summarised in Table 1, in conjunction with binding data for olanzapine and quetiapine, two other atypical antipsychotics discussed in this paper, as well as haloperidol, the prototypical "typical" antipsychotic. Examination of some of clozapine and zotepine's shared receptors in rats reveals that the rank order of decreasing binding affinity for clozapine was H_1, 5-HT_{2A}, α_1, Muscarinic, D_1, α_2 and D_2; whilst for zotepine the rank order was 5-HT_{2A}, H_1, α_1, D_2, D_1, Muscarinic, and α_2. Similar rank potencies are shown for the human binding data (see Table 1). The clearest difference between clozapine and zotepine is the relatively greater affinity of zotepine for D_2 receptors in both rats and humans. Thus, clozapine and zotepine share similar, although not identical, in vitro binding profiles. However, zotepine differs from clozapine and other "atypical" antipsychotics (such as olanzapine and ziprasidone), in that it has affinity for the noradrenaline (NA) transporter (the Kis for zotepine and clozapine, respectively, for the NA transporter being 21 nM and >1 μM), and zotepine causes marked elevation of cortical extracellular NA when assessed with in vivo microdialysis (Rowley et al., 1998).

Table 1
In vitro binding affinities (Ki values nm/l)

Drug	Receptor						
	D_1	D_2	5-HT_{2A}	α_1	α_2	Muscarinic	H_1
A. Rat data[a]							
Zotepine	33.7	9	2.5	4	704	196	2.7
C1ozapine	252	363	8.3	11.7	276	32.6	7.6
Quetiapine	390	69	82	4.5	1100	56	21
Olanzapine	10	2.1	1.9	7.3	140	2.1	5.6
Haloperidol	15	0.82	28	7.3	1600	570	>730
B. Human data[b]							
Zotepine	NA	8.1	2.6	7.3	180	330	3.3
C1ozapine	NA	210	2.6	6.8	15	9.1	3.1
Quetiapine	NA	770	31	8.1	80	1400	19
Olanzapine	NA	20	1.48	44	280	36	0.08
Haloperidol	NA	2.6	61	17	600	>10000	260

[a] Data for zotepine and clozapine are from Needham et al. (1996). Data for all other drugs are from Arnt and Skarsfeldt (1998).

[b] Data for all drugs are from Richelson and Souder (2000). NA = not available.

In summary, zotepine shares many properties with the prototypical atypical antipsychotic clozapine. However, it also differs from it. The studies reported here were concerned with the comparative analysis of the atypical antipsychotics zotepine, clozapine and quetiapine in the drug discrimination bioassay in rats in order to allow in vivo comparisons to be made between these various drugs.

Clozapine discrimination has now been characterised in detail in various species (Carey and Bergman, 1997; Goudie and Taylor, 1998; Goudie et al., 1998a,b; 2001; Millan et al., 1999, 2000; Moore et al., 1992; Porter et al., 1999, 2000b). It has been hypothesised (Carey and Bergman, 1997; Goudie et al., 1998a,b; Goudie and Taylor, 1998; Millan et al., 1999; Tang et al., 1997) that clozapine induces a "compound" stimulus (cue) requiring concurrent actions at various receptors. This hypothesis is based on two lines of evidence. Firstly, antipsychotics or putative novel antipsychotics which generalize fully to clozapine, including JL 13 (Bruhwyler et al., 1997), PNU-96415E (Tang et al., 1997), S16924 (Millan et al., 1999), S18327 (Millan et al., 2000) and quetiapine (Carey and Bergman, 1997; Goudie and Taylor, 1998; Millan et al., 1999) all resemble clozapine in having concurrent actions at many receptors. In contrast, older typical antipsychotics with more restricted binding profiles, such as haloperidol (see Table 1) and the newer drugs risperidone and sertindole (predominantly D_2/5-HT_{2A}/α_1 antagonists), and amisulpride (a selective $D_{2/3}$ antagonist) do not generalize fully to clozapine (Carey and Bergman, 1997; Goudie and Taylor, 1998; Millan et al., 1999; although cf. Porter et al., 2000b) Secondly, selective ligands at very many different types of receptors typically do not generalize to clozapine (Goudie et al., 1998a,b; Millan et al., 1999; Porter et al., 1999; Wiley and Porter, 1992). The only exception to this rule is the antimuscarinic scopolamine, which has been found to generalise fully (Kelley and Porter, 1997; Goudie et al., 1998a,b). However, this finding does not in itself refute the hypothesis that the clozapine cue is a compound cue, since the individual components of compound cues can, under specific circumstances, induce full generalisation to the compound cue itself (see Goudie et al., 1998a,b, in press; Goudie and Smith, 1999, for full discussions of this issue). In support of the compound cue hypothesis, it has been reported that rats discriminating the putative antipsychotic S16924, which also acts like clozapine at many receptors, generalize fully to clozapine, and that rats discriminating clozapine generalise reciprocally to S16924 (Millan et al., 1999). Furthermore, rats discriminating olanzapine, which also acts at many receptors (see Table 1) generalise to clozapine (Porter and Strong, 1996; Porter et al., 2000a).

Recently we have characterised in considerable detail the discriminative properties of quetiapine (Smith and Goudie, 2002; Goudie et al., in press). Rats discriminating quetiapine showed full generalisation in tests with the atypical antipsychotics clozapine, olanzapine and risperidone, no generalisation being seen with the typical anti-

psychotics chlorpromazine, haloperidol and loxapine. On the basis of these data, we hypothesised that the quetiapine stimulus resembles the clozapine stimulus in being a compound cue (Smith and Goudie, 2002). To investigate this further (Goudie et al., in press) we tested a wide range of agents with selective actions at various receptors (α_1, α_2, H_1, D_1, D_2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_{1A} and benzodiazepine) in rats discriminating quetiapine. None of these agents induced full generalisation to quetiapine, supporting the compound cue hypothesis. The overall pattern of generalisation seen in rats discriminating quetiapine resembled that seen in rats discriminating clozapine (Goudie et al., in press), despite the fact that the binding profiles of these drugs differ, quetiapine, in contrast to clozapine, having highest affinity for α_1 receptors (see Table 1).

The studies reported here were concerned with extending this work to characterise the stimulus properties of zotepine and compare them with those of both clozapine and quetiapine. To this end zotepine was initially studied in rats discriminating clozapine, and then rats discriminating quetiapine. Finally, an attempt was made to train zotepine itself as a discriminative stimulus.

2. Methods

The work reported here was conducted in accord with The Animals (Scientific Procedures) Act 1986 under UK Home Office licensing.

2.1. Experiment 1

2.1.1. Subjects

Twenty-seven individually housed female Wistar rats (approximately 300 g) were maintained on a restricted diet (Bantin and Kingman, UK) which kept their weights at approximately 80% of ad lib levels. They had unlimited access to water except during operant sessions which were run 5 days/week. The animals were divided into two groups trained to discriminate clozapine at 2 mg/kg ip ($n = 13$) and 5 mg/kg ip ($n = 14$), respectively.

2.1.2. Apparatus

Rats were trained to respond for 45-mg food pellet rewards (Noyes, Sandown Scientific, UK) in standard two-lever computer-controlled Colbourne Instruments Skinner boxes.

2.1.3. Procedure

This was a drug versus vehicle Fixed Ratio 30 quantal operant drug discrimination assay, as previously described (Goudie et al., 1998a,b; Goudie and Taylor, 1998). On any training day, rats received either clozapine or vehicle. The 5 mg/kg training dose of clozapine has previously been shown to be discriminable in rats in a number of studies (e.g., Kelley and Porter, 1997; Goudie and Taylor, 1998; Millan et al., 1999; see Goudie and Smith, 1999, for review). Lower training doses do not appear to have been studied previously in detail, although Browne and Koe (1992) and Porter et al. (2000b) trained rats on 3.2 and 1.25 mg/kg of clozapine, respectively. In unpublished studies we were unable to train rats on 1 mg/kg of clozapine. Thus, we consider 2 mg/kg of clozapine to be the lowest dose that rats can discriminate in our laboratory. Since we hypothesised that zotepine might generalise to clozapine, we assessed the actions of clozapine and zotepine in two groups of rats trained to discriminate clozapine at 2 and 5 mg/kg, respectively. The extent to which generalisation is seen in drug discrimination assays is dependent upon the training dose utilised, the generalisation dose–effect curve typically shifts to the left in animals trained on a lower dose, due to their greater sensitivity to the training drug (e.g., Colpaert et al., 1980a). Although clozapine discrimination has been studied extensively, systematic studies of the effect of clozapine training dose on its discriminative properties, as described here, have not been conducted, with the important exception of the study of Porter et al. (2000b), who reported that, with a low training dose (1.25 mg/kg) of clozapine in rats, atypical antipsychotics such as olanzapine and risperidone which did not generalise fully to a higher 5 mg/kg training dose of clozapine (e.g., Goudie and Taylor, 1998) did generalise fully to the lower dose. Thus, we hypothesised that if zotepine generalised to clozapine, we might see more generalisation in rats trained on the lower dose of clozapine.

During training clozapine injections were administered in a pseudorandom sequence in which drug and vehicle never occurred successively more than twice. Animals were trained so that olfactory cues from rats run in previous sessions on any day could not confound the discrimination (Extance and Goudie, 1981). All training injections of clozapine or vehicle were administered 30 min before operant sessions, which were of 15 min duration. When they were injected with clozapine, rats were rewarded for responding on one lever, responding on the other lever had no consequences. When injected with vehicle, rats were rewarded for responding on the alternative lever only. On any trial, accuracy of lever selection was assessed in terms of the total responses made on both levers prior to the first reward—termed the FRF (responses to **F**irst **R**ein**F**orcement). If the FRF was 30, the rat had made a 'perfect' lever selection. If the FRF was >59, the rat had made an incorrect selection. When all animals were reliably discriminating clozapine (the group levels of accuracy of discrimination were consistently above 85% correct and all animals had made at least 8/10 consecutive correct lever selections), generalisation tests with clozapine and zotepine were initiated. Routine test days were typically run with at least two interspersed training days to ensure that the discrimination was maintained at a high level prior to each test. Planned tests were not run if a group's baseline level of accuracy

of lever selection fell below 85% on the prior day. On test days, rats were rewarded throughout operant sessions for responding on the lever on which they first accumulated 30 responses. Thus, on test days, if a rat made a lever selection (made 30 responses on either lever), it was defined as having selected either the drug or vehicle lever. For each group as a whole, it was thus possible to define the percentage of animals selecting the drug lever. In addition, on test days it was possible to assess drug actions on response rate. The total number of responses made by each rat was expressed as a percentage of the total number of responses recorded on the most recent vehicle training session. In generalisation tests, zotepine was administered 4 h before test sessions due to its slow onset pharmacokinetic/pharmacodynamic profile, such that its potency in inhibiting apomorphine-induced climbing is actually greater 4 h post injection than 30 min post injection, an effect not seen with clozapine (Needham et al., 1996). Clozapine was administered 30 min before tests, as during training. Drugs were tested with at least three doses of both compounds in both training groups, administered in random order. Each set of drug tests also included a vehicle test to demonstrate the absence of drug lever selection in vehicle tests and to obtain baseline data to assess drug effects on response rate.

2.1.4. Statistics

Generalisation data were analysed using log/probit bioassay analyses (SPSS for Windows; see Fasciano et al., 1997, for a previous example of such analysis related to drug discrimination). These analyses allowed computation of (i) EDs_{50} and tests of significant differences in these EDs_{50}; and (ii) Significant deviations from parallelism for generalisation curves. Response rates were analysed using repeated measures ANOVAs followed by post hoc Dunnett's tests.

2.1.5. Materials (for all studies)

Clozapine base (Novartis, Switzerland) zotepine base (BASF Pharma Research, Nottingham, UK) and quetiapine fumarate (AstraZeneca Pharmaceuticals, USA) were administered intraperitoneally, having first been dissolved in a few drops of 0.1 N HCl, diluted with distilled water and buffered back with NaOH to a pH around 5.5 and injected at a volume of 2 ml/kg. Drugs were made up as salts or bases, in the forms indicated above.

2.2. Experiment 2

The procedures used were exactly as in Experiment 1 unless specified. Eighteen female Wistar rats were trained to discriminate quetiapine at 10 mg/kg ip before tests with quetiapine and zotepine. This training dose was chosen as it has been found to induce full generalisation in rats trained to discriminate clozapine at 5 mg/kg (Goudie and Taylor, 1998; Millan et al., 1999), and because we have characterised in detail the discriminative properties of this training dose in rats (Smith and Goudie, 2002; Goudie et al., in press). Quetiapine (AstraZeneca Pharmaceuticals, USA) was administered intraperitoneally 30 min before training and generalisation tests. It was dissolved in a few drops of 0.1 N HCl, diluted with distilled water and buffered back with NaOH to a pH around 5.5 and injected at a volume of 2 ml/kg. As in Experiment 1, zotepine was administered 4 h before generalisation tests due to its slow onset pharmacokinetic/pharmacodynamic profile (Needham et al., 1996).

2.3. Experiment 3

In this experiment, an attempt was made to train zotepine as a discriminative stimulus. Fourteen female Wistar rats were trained using the procedures described. Zotepine was administered 4 h before training sessions, as in both prior experiments. The initial training dose of zotepine was 1 mg/kg. This was increased to 2 mg/kg after 70 training sessions. Higher training doses of zotepine could not be used due to rate suppressant actions of the drug in drug-naive rats. Even with doses of 1 and 2 mg/kg some rats failed to make a lever selection at all (i.e., accumulate 30 responses on either lever) on a few training days.

3. Results

3.1. Experiment 1

The 5 mg/kg clozapine discrimination was learned relatively rapidly. After 50 training sessions the group had achieved a consistent daily level of accuracy of correct lever selection of 85% which was maintained throughout the study. The 2 mg/kg clozapine discrimination took somewhat longer to learn (approximately 80 sessions to a group level of 85% daily accuracy).

Fig. 1 shows the results of the clozapine generalisation tests. In both vehicle tests (0 mg/kg) there was no drug lever selection at all and response rates were approximately 100% of baseline levels. As expected, clozapine induced dose-related full generalisation in rats trained on both doses of clozapine. The generalisation curve was shifted to the left in the 2 mg/kg training group relative to the 5 mg/kg group. The ED_{50} for the 5 mg/kg clozapine group was 1.41 mg/kg. The ED_{50} for the 2 mg/kg clozapine group was 0.58 mg/kg. Thus, the generalisation curve was shifted 2.4-fold to the left in the lower training dose group. The two dose–effect curves did not deviate significantly from parallelism, but the ED_{50}s were significantly different ($P<.05$). In both groups there was no significant drug effect on response rate [$F(3,55)=2.58$, $P=.07$ for the high clozapine dose group, and $F(4,64)=0.93$, $P=.45$ for the low dose group]. Thus, clozapine was discriminated without any significant effects on operant behaviour.

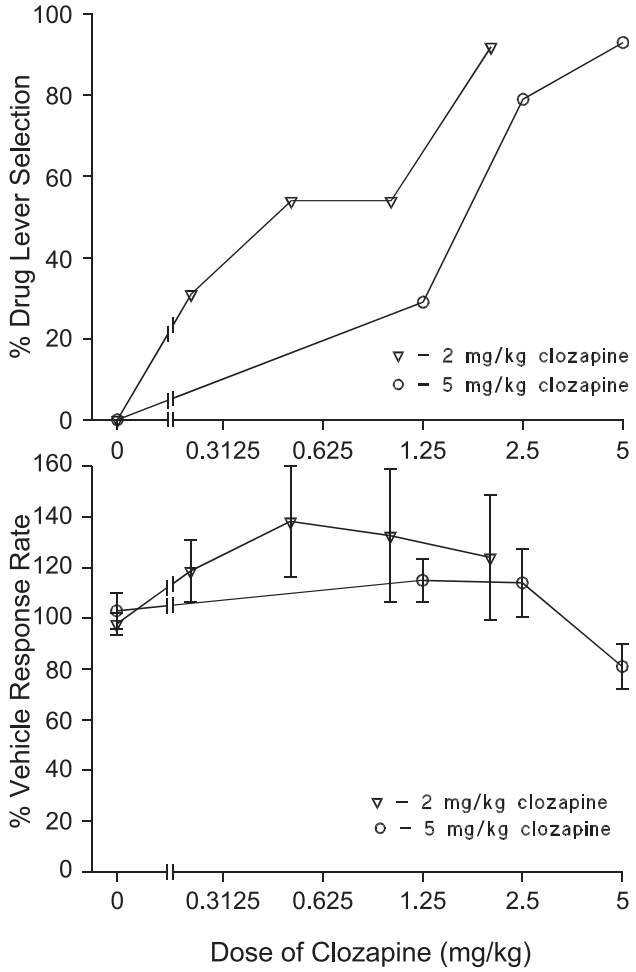

Fig. 1. Upper panel: Clozapine generalisation curves in groups of rats (ns = 13–14) trained to discriminate clozapine at 2 mg/kg (triangles) and 5 mg/kg (circles). Vehicle test days are shown as 0 mg/kg doses for both groups and clozapine dose is shown on a logarithmic scale. Lower panel: Effects of clozapine on response rate (expressed as a percentage of that observed on the most recently preceding vehicle training day). The data shown are group means (± S.E.). The group mean (± S.E.) absolute response numbers obtained in the 15 min duration training sessions immediately before the relevant vehicle tests were 748 (131) for the 5 mg/kg trained group and 1640 (189) for the 2 mg/kg trained group.

Fig. 2 shows the results of the zotepine tests. In both vehicle (0 mg/kg) tests there was minimal (< 20%) selection of the drug lever, and response rates were approximately 100% of baseline levels. In the 5 mg/kg clozapine training dose group zotepine induced dose-related generalisation, with a maximal level of 50% generalisation at the highest dose that could be tested (5 mg/kg) due to rate-suppressant actions of zotepine. The ED_{50} for zotepine in these animals was 5.56 mg/kg. In the 2 mg/kg clozapine-trained animals, zotepine induced dose-related full generalisation. The ED_{50} was 0.69 mg/kg. The two dose–effect curves did not deviate significantly from parallelism, but the two EDs_{50} were significantly different ($P < .05$). Thus, as in the tests with clozapine, the generalisation dose–response curve was shifted significantly in parallel to the left in the rats trained on the 2 mg/kg dose of clozapine, in this case 8.1-fold. In direct contrast to the results from the clozapine tests, responding was suppressed by zotepine in a dose-related fashion in rats trained on both clozapine training doses (see lower panels of Fig. 2), with significant effects [$F(3,55) = 15.13$, $P = .0001$ for the high clozapine training dose group, and $F(3,51) = 15.01$, $P = .0001$ for the low clozapine training dose group]. Post hoc tests showed significance relative to the appropriate vehicle baseline values at 5 mg/kg of zotepine in both groups of rats. A two-factor [2 (groups) × 2 (doses)] ANOVA with repeated measures on the zotepine doses of 1 and 5 mg/kg (i.e., the doses which appeared to suppress responding) revealed a highly significant dose effect [$F(1,25) = 63.62$; $P < .001$], but no significant difference

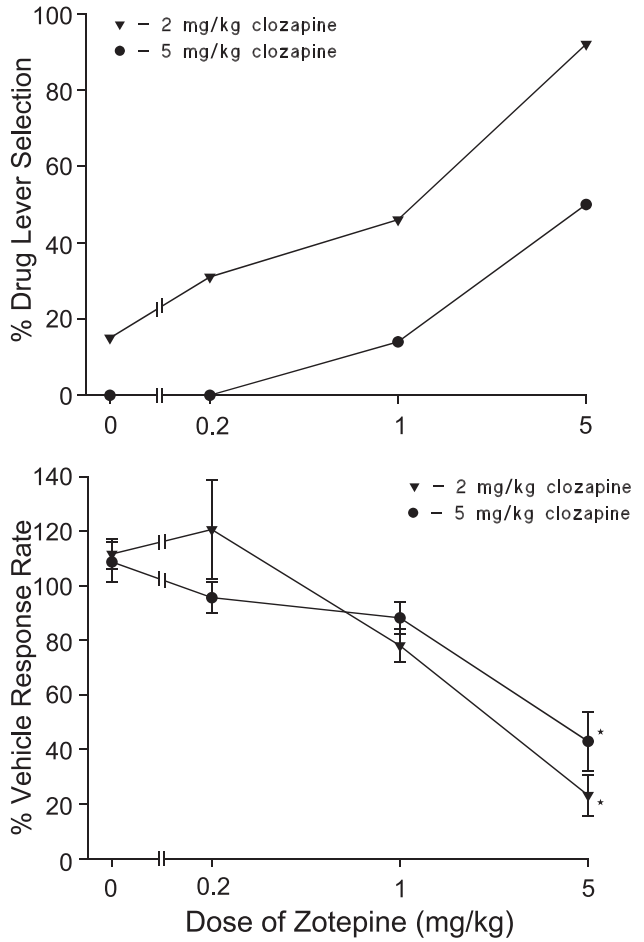

Fig. 2. Upper panel: Zotepine generalisation curves in groups of rats (ns = 13–14) trained to discriminate clozapine at 2 mg/kg (triangles) and 5 mg/kg (circles). Vehicle test days are shown as 0 mg/kg for both groups and zotepine dose is shown on a logarithmic scale. Lower panel: Effects of zotepine on response rate (expressed as a percentage of that observed on the most recent preceding vehicle training day). The data shown are group means (± S.E.). Points marked by asterisks are significantly different from relevant vehicle data by Dunnett's test after ANOVA. At all doses all rats made a lever selection. The group mean (± S.E.) absolute response numbers obtained in the 15-min duration training sessions immediately before the relevant vehicle tests were 1141 (169) for the 5 mg/kg trained group and 1498 (182) for the 2 mg/kg trained group.

between the groups, and no significant interaction. Thus, the rate-suppressant actions of zotepine did not differ significantly between the two groups in contrast to the differences seen with the discriminative stimulus properties.

3.2. Experiment 2

The quetiapine discrimination was learned relatively rapidly. After 50 training sessions the group had achieved a consistent daily level of accuracy of correct lever selection of 85% which was maintained throughout the study (see Smith and Goudie, 2002, for data on the acquisition of quetiapine discrimination at the 10 mg/kg training dose).

Fig. 3 shows the results of generalisation tests conducted in the quetiapine trained rats with quetiapine and zotepine. Although 18 rats were trained to discriminate quetiapine and tested with quetiapine, 1 rat was dropped for the tests with zotepine due to inaccurate responding just before these tests. In both vehicle tests (0 mg/kg) there was minimal (< 10%) drug lever selection and response rates were approximately 100% of baseline levels. Quetiapine induced dose-related full generalisation to itself, as expected. The ED_{50} was 2.32 mg/kg. Zotepine did not generalise fully, the maximal level of generalisation being 54%. The ED_{50} was 1.74 mg/kg. Both quetiapine and zotepine induced dose-related significant response suppression, see lower panel of Fig. 3 [$F(3,71 = 7.42$, $P=.0003$ for quetiapine; $F(3,67) = 69.56$, $P=.0001$ for zotepine]. Quetiapine only induced full generalisation at the training dose (10 mg/kg) which suppressed responding significantly. At the two highest does of zotepine tested a few rats did not make a lever selection at all due to drug-induced suppression of responding (see Fig. 3). At the highest dose of zotepine tested (3 mg/kg) responding was suppressed to as low as 27% of baseline. Thus, it was not possible to test higher doses.

3.3. Experiment 3

An attempt was made to train the zotepine discriminative stimulus in 14 rats over as many as 150 training sessions. Although drug lever selection for the group was consistently above chance (50%) levels after 50 training sessions, it proved impossible to train the discrimination to a consistently high and reliable level of accuracy. Even after as many as 125 training sessions on some training days the overall group level of accuracy of lever selection actually fell below the chance (50%) level. After 100 training sessions an attempt was made to select out for analysis and possible subsequent testing a subset of the best 8 of the 14 rats which showed the highest level of accuracy of lever selection (cf. Porter et al., 2000a). These rats had all reached a criterion of having, at some time during the prior 100 training sessions, made 9 out of 10 consecutive correct lever selections. However, even for these selected rats, performance was subsequently unstable and unreliable, and at times the subgroup's level of accuracy of lever selection dropped as low as 62% correct. Thus, after as many as 150 training sessions this study was terminated and we concluded that, in contrast to the results obtained with both clozapine and quetiapine, it was not possible to train zotepine as a reliable discriminative stimulus.

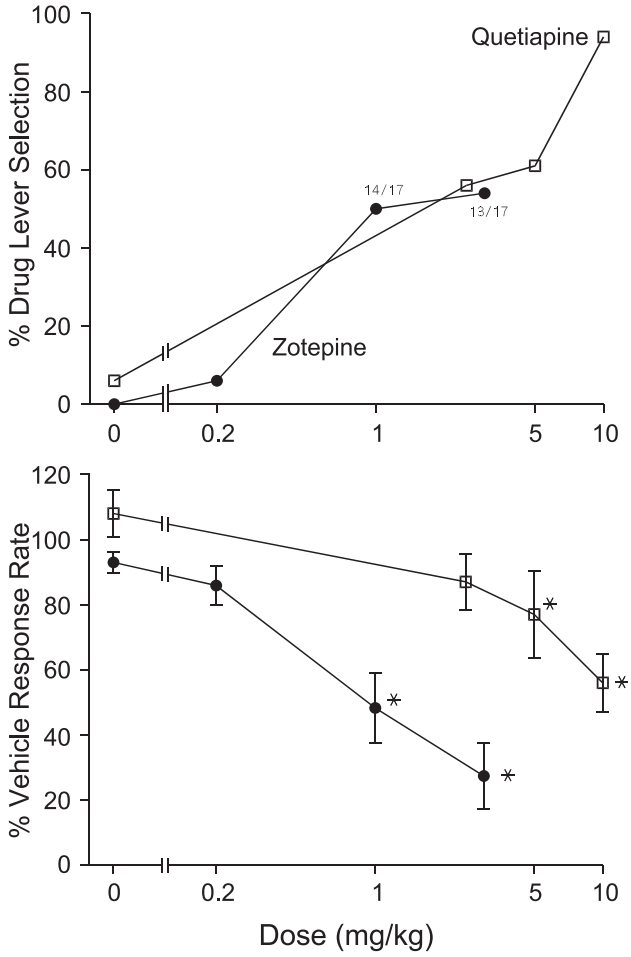

Fig. 3. Upper panel: Quetiapine and zotepine generalisation curves in rats trained to discriminate quetiapine at 10 mg/kg. Vehicle test days are shown as 0 mg/kg. Dose is shown on a logarithmic scale. At the two highest doses of zotepine tested only 14 and 13 of the 17 tested rats made a lever selection. At all other doses all rats made a lever selection. Lower panel: Effects of quetiapine and zotepine on response rate (expressed as a percentage of that observed on the most recent preceding vehicle training day). The data shown are group means (± S.E.). Points marked by asterisks are significantly different from relevant vehicle data by Dunnett's test after ANOVA. The group mean (± S.E.) absolute response numbers obtained in the 150-min duration training sessions immediately before the relevant vehicle tests were 1976 (158) for the quetiapine vehicle test and 2025 (153) for the zotepine vehicle test.

4. Discussion

4.1. Experiment 1

Clozapine and zotepine clearly had similar discriminative stimulus properties. In clozapine-trained rats cloza-

pine induced full generalisation in both groups. The ED_{50} was significantly lower in the group trained on the lower dose of clozapine, in accord with evidence that as training dose decreases, generalisation gradients shift to the left (Colpaert et al., 1980b). The generalisation curve in the rats trained on the lower dose of clozapine shifted in parallel, demonstrating that the two groups differed quantitatively, rather than qualitatively, in terms of their sensitivity to clozapine. Zotepine induced full substitution in the rats trained on the lower clozapine dose, and 50% substitution in the rats trained on the higher dose. As for clozapine, the ED_{50} was significantly lower in the rats trained on the lower dose and the generalisation curve was shifted in parallel to the left in the lower training dose group again implying that the two groups simply differed quantitatively in terms of their sensitivity to zotepine.

The data obtained with zotepine resemble closely the findings of Porter et al. (2000b), who reported that a number of atypical antipsychotics (olanzapine, sertindole and risperidone) which failed to generalise fully to a high clozapine training dose did to a lower training dose. Since typical antipsychotics (e.g., haloperidol, chlorpromazine and fluphenazine) did not generalise to the low training dose of clozapine, Porter et al. (2000b) concluded that a discrimination involving a low dose of clozapine provides a selective assay for dissociating many atypical from typical antipsychotics. Since we have previously reported that haloperidol does not generalise to either a low or a high training dose of clozapine (Goudie et al., 1998a,b), our findings accord fully with the conclusion of Porter et al. (2000b) that a low, but not a high, training dose of clozapine may dissociate many atypical clozapine-like antipsychotics from typical antipsychotics.

Since zotepine resembles clozapine in having affinity for many receptors, these data accord with the hypothesis that the clozapine cue is a "compound" cue (see Introduction). It may therefore be hypothesised that zotepine probably also induces a compound cue, as it generalises fully to clozapine.

However, although clozapine and zotepine share similar discriminative properties, there were clear differences between the drugs. Although clozapine induced full generalisation at doses that did not suppress responding significantly, this was not the case for zotepine. Clozapine is well known to suppress responding acutely at doses around 2–5 mg/kg in rats (e.g., Sanger and Perrault, 1995), although tolerance develops quite rapidly to this effect (Varvel et al., 2002; Goudie et al., unpublished). Thus, the lack of clozapine-induced response suppression in the clozapine-trained rats was due presumably to the development of tolerance to clozapine during training (see also Goudie and Taylor, 1998; Varvel et al., 2002). The full tolerance, which developed to clozapine, clearly did not confer full cross-tolerance to zotepine. Thus, zotepine and clozapine do not have identical overall profiles of action in drug discrimination assays.

In a previous study (Goudie and Taylor, 1998), in which various novel antipsychotics were studied in rats discriminating clozapine at 5 mg/kg, we reported the following levels of maximal generalisation in tests with various novel atypical antipsychotics: risperidone (20%), amisulpiride (28%), olanzapine (38%), sertindole (50%), quetiapine (83%) and clozapine (100%). Similar data have been reported in monkeys by Carey and Bergman (1997). Since in these rats zotepine only induced 50% maximal generalisation in the 5 mg/kg training group in this study, the data can be interpreted as suggesting that zotepine resembles clozapine much more than risperidone and amisulpiride, slightly more than olanzapine; to the same extent as sertindole; but less than quetiapine and clozapine itself. The failure of zotepine to generalise fully to clozapine at 5 mg/kg in this study, in contrast to clozapine itself and quetiapine, thus suggests that clozapine and quetiapine both differ subtly in their cue properties from zotepine. This difference may possibly be due to zotepine's unique ability as an antipsychotic to inhibit noradrenaline uptake (Rowley et al., 1998), since antagonist actions at $alpha_1$-noradrenergic receptors may play a significant role in the clozapine cue, the $alpha_1$-noradrenergic antagonist prazosin having been reported consistently to generalise partially to clozapine (Goudie et al., 1998a,b), and since noradrenaline uptake inhibition would be expected to enhance NA levels and thus to have an effect that would probably be opposite to that induced by $alpha_1$-noradrenergic antagonism. Alternatively, the failure of zotepine to generalise fully to the 5 mg/kg training dose of clozapine may simply be due to fact that zotepine, in contrast to clozapine, suppressed responding. This action of zotepine could have limited its ability to mimic clozapine in two different ways: (i) by inducing drug effects that "masked" the stimulus properties of zotepine; or (ii) by limiting the doses of zotepine that could be tested. If it had been possible to test higher doses of zotepine full generalisation might have been observed to the high clozapine dose. In this context it is notable that zotepine differs from clozapine in having higher affinity for D_2 receptors (see Table 1). Antagonist drug actions at such receptors are well known to be involved in response rate suppression (e.g., Varvel et al., 2002). Thus, the greater inherent D_2 antagonist actions of zotepine may have limited its ability to mimic clozapine. In accord with this hypothesis, Carey and Bergman (1997) reported that the ability of olanzapine (which also has high affinity for D2 receptors, see Table 1) to generalise to clozapine could be enhanced by administering a D_2 agonist.

4.2. Experiment 2

In this study quetiapine induced full generalisation to itself, as expected, although such generalisation was only seen at a dose which suppressed responding. Zotepine

induced dose-related but incomplete generalisation (maximum = 54%). The quetiapine cue clearly differs from the clozapine cue, in that in trained rats clozapine, unlike quetiapine, does not suppress responding at doses which induce full generalisation. These data, plus the observation from Experiment 1 that zotepine suppressed responding in clozapine experienced rats, accord with evidence that clozapine may be unique amongst novel atypical antipsychotics (including quetiapine, olanzapine and risperidone) in showing tolerance to its suppressant actions on operant responding in rats (Varvel et al., 2002). The precise clinical relevance of this observation is at present unclear, although Varvel et al. (2002) have suggested that it may be related to some of clozapine's unique clinical actions.

We have reported that, at the training dose used in this study, rats discriminating quetiapine show full generalisation to clozapine, olanzapine and risperidone, no generalisation being seen with chlorpromazine, haloperidol, and loxapine (Smith and Goudie, 2002). Thus, this specific training dose of quetiapine appears to differentiate atypical from typical antipsychotics, in a fashion very similar to a low training dose of clozapine (Porter et al., 2000b). The finding that zotepine only induced 54% generalisation to quetiapine thus appears somewhat surprising. Based upon the findings of Goudie and Taylor (1998) and Experiment 1 we suggested above that zotepine resembles clozapine more than risperidone and olanzapine, since it generalised to a greater extent to a high dose clozapine cue. However, in terms of generalisation to quetiapine, both these drugs actually resembled clozapine more then zotepine, since they both generalised fully to quetiapine (Smith and Goudie, 2002). The failure of zotepine to generalise fully to quetiapine may possibly be attributable to its relatively high D_2 affinity (see Table 1), which might have induced operant response rate suppression and limited generalisation.[1] If it had been possible to test higher doses of zotepine they might have induced full generalisation to quetiapine. Alternatively, as described above, rate suppressant effects of zotepine might have induced stimuli which "masked" the zotepine stimulus. A further possible explanation for the failure of zotepine to generalize fully to quetiapine may relate to zotepine's unique action as an inhibitor of NA uptake (Rowley et al., 1998). As described for the clozapine cue, antagonist actions at alpha$_1$-noradrenergic receptors may also play a significant role in the quetiapine cue (Goudie et al., in press) and NA uptake inhibition might be expected to induce effects opposite to such antagonist actions and thus possibly limit generalisation.

[1] Olanzapine also possesses high D_2 affinity (see Table 1). Nevertheless it, in contrast to zotepine, generalised fully to quetiapine (Smith and Goudie, 2002). In the case of olanzapine, the effects of its high D_2 affinity have may been offset by intrinsic muscarinic antagonist actions of the drug, which zotepine lacks (see Table 1).

4.3. Experiment 3

It was impossible to train zotepine as a reliable discriminative stimulus. This was not due to the use of doses which do not possess stimulus properties, as the doses used (1 and subsequently 2 mg/kg) induced clear but incomplete generalisation to a low dose clozapine stimulus and also to the quetiapine stimulus. Thus, the zotepine stimulus clearly differs from both the clozapine and quetiapine stimuli. A possible explanation for such findings again lies in the relatively high D_2 receptor affinity of zotepine. It has been known for many years that D_2 antagonists such as haloperidol are difficult to train as discriminative stimuli (see Goudie and Smith, 1999, for review), although such discriminations have occasionally been trained effectively (McElroy et al., 1989), and rats trained to discriminate the $D_{2/3}$ antagonist tiapride (albeit only after extensive training) showed full generalisation to haloperidol and related agents (sulpiride, raclopride and pimozide—Cohen et al., 1997). Thus, D_2 antagonists are discriminable, although only with difficulty. It is thus possible that D_2 antagonist actions of compound cues may limit the discriminability of such cues. In support of this hypothesis, Porter et al. (2000a) reported that when attempts were made to train olanzapine as a stimulus, a drug which also has relatively high D_2 affinity (see Table 1), it was only possible to train a proportion of the rats studied. Furthermore, as described above, Carey and Bergman (1997) reported that the ability of olanzapine to generalise to clozapine was enhanced by administering a D_2 agonist. Thus, we suggest that the difficulties encountered in training zotepine (and olanzapine) as discriminative stimuli were probably due to the relatively high D_2 affinities of these drugs. High D_2 affinity may limit discriminability by inducing response rate suppression, which may retard learning of a discrimination by either reducing reinforcement, or by inducing stimuli which "mask" the drug stimulus, or finally, and more directly, by attenuating the "perception" of a drug's discriminative properties. At present it is not possible to differentiate between these alternative hypotheses.

4.4. Overall conclusions

The data reported here support a number of conclusions about the discriminative properties of zotepine and of novel atypical antipsychotics in general: (i) The zotepine stimulus is similar to, but not identical with, the clozapine stimulus. Zotepine only generalises fully to a low (2 mg/kg) training dose of clozapine, and even then it does not mimic clozapine fully, as it, unlike clozapine, suppresses responding significantly in clozapine experienced rats; (ii) The generalisation seen between zotepine and clozapine is compatible with the hypothesis that the zotepine stimulus resembles the clozapine stimulus in being a compound cue; (iii) The failure of zotepine to

mimic clozapine fully at a high (5 mg/kg) training dose, whilst generalising fully to the low training dose shows that it is similar to a number of other (olanzapine, sertindole and risperidone), atypical antipsychotics, which fail to generalise fully to a high training dose of clozapine but generalise fully to a low training dose (Porter et al., 2000b); (iv) As typical antipsychotics such as haloperidol, chlorpromazine and others do not generalise to the low training dose of clozapine (Porter et al., 2000b; Goudie et al., 1998a,b), the low dose clozapine stimulus appears to be an effective in vivo bioassay to dissociate typical from most novel atypical antipsychotics, as suggested originally by Porter et al. (2000b); (v) The subtle differences observed between the clozapine and zotepine stimuli may be related to either the unique ability of zotepine to block NA uptake, or to the more marked affinity of zotepine for D_2 receptors compared to clozapine, which may limit its ability to mimic clozapine; (vi) Zotepine only mimics quetiapine up to a level of 54% in the drug discrimination bioassay. This finding was unexpected, since quetiapine and clozapine generalise reciprocally (Goudie and Taylor, 1998; Smith and Goudie, 2002) and zotepine generalised fully to (low dose) clozapine. This finding may also be related either to zotepine's unique ability to inhibit NA uptake, or to its rate suppressant actions, which may be due to the relatively high D_2 affinity of zotepine; (vii) The quetiapine stimulus differs from the clozapine stimulus, in that quetiapine, unlike clozapine, only induces full generalisation to itself at rate suppressant doses. This observation, in conjunction with the observation that clozapine and zotepine differ in their effects on response rate in clozapine experienced rats supports a recent suggestion that clozapine may be unique among many atypical antipsychotics in showing tolerance development in operant studies in rats (Varvel et al., 2002); (viii) Although zotepine clearly possesses discriminative stimulus properties, it is not possible to train zotepine as a reliable stimulus itself. The difficulties encountered in training the zotepine stimulus, in contrast to the clozapine and the quetiapine stimuli may be due to its more marked D_2 affinity.

4.5. General discussion

Collectively these data demonstrate that both similarities and differences between the atypical antipsychotics clozapine, quetiapine and zotepine can be demonstrated in drug discrimination bioassays in rats. A similar conclusion about the clozapine and olanzapine cues was reached by Porter et al. (2000a), based upon studies of the stimulus properties of olanzapine; since although clozapine generalised to olanzapine, some antipsychotic drugs which generalised to olanzapine (chlorpromazine and thioridazine) did not generalise to clozapine, indicating that the clozapine and olanzapine cues differ. These findings therefore support the suggestion that atypical antipsychotics do not form a homogeneous class (Arnt and Skarsfeldt, 1998). Despite their overlapping pharmacological profiles, to some extent each drug must be considered a unique agent.

However, recent evidence for common actions of various atypical antipsychotics in drug discrimination tasks comes from a report that many such drugs (clozapine, quetiapine, risperidone, ziprasidone, S16924 and S18327) all generalise to MDL 100,907, which induces a cue which is mediated specifically by antagonist actions at 5-HT_{2A} receptors (Dekeyne et al., 2003). MDL 100,907 does not, however, generalise to either clozapine (Goudie et al., 1998a,b) or quetiapine (Goudie et al., in press). Thus, it appears that the 5-HT_{2A} antagonist component of the compound clozapine and quetiapine cues is overshadowed by other, more salient, components when the drugs are used as training stimuli. This suggests (Dekeyne et al., 2003) that common actions of "atypical antipsychotics are more likely to be detected in drug discrimination tasks when specific ligands are used as training stimuli, whilst differential actions are more likely to be detected when atypical antipsychotics are used as training stimuli, as in the studies reported here.

In so far as the zotepine stimulus is concerned, we interpret the data presented here as showing that the stimulus properties of zotepine resemble those of both clozapine and quetiapine to considerable, but incomplete extents. Such data do not prove that these agent will necessarily have similar actions as antipsychotics, as there is no direct evidence that the stimulus properties of such drugs map directly onto their clinical antipsychotic actions (see Goudie et al., 1998a,b; Goudie and Smith, 1999; Goudie et al., in press, for detailed discussions of this issue). However, despite this important caveat, it is reasonable to conclude that, given the similar clinical profiles and similar actions of clozapine and zotepine in various preclinical tests (see Introduction), the data reported here add to a growing body of evidence that zotepine resembles clozapine. However, zotepine's ability to block NA uptake differentiates it from clozapine and other atypical antipsychotics (Rowley et al., 1998). Recent preclinical evidence (Linner et al., 2002) suggests that the combination of a noradrenaline uptake inhibitor and the $D_{2/3}$ antagonist raclopride generates a profile of drug action in various assays considered indicative of atypical antipsychotic actions. Thus, the ability of zotepine to enhance NA uptake may account, at least in part, for its atypical profile, although this action may well differentiate zotepine from clozapine and other novel antipsychotics. Further comparative studies of zotepine with other novel antipsychotics are merited in both preclinical and clinical settings.

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