Pharmacology Biochemistry and Behavior, Vol. 56, No. 2, pp. 317–324, 1997

0091-3057/97 $17.00 + .00

PII S0091-3057(96)00293-6

Anticonflict Effect of Alpidem as Compared with the Benzodiazepine Alprazolam in Rats

MARTINE HASCOËT[1] AND MICHEL BOURIN

Department of Pharmacology and GIS Médicament, Faculty of Medicine, 1 rue G. Veil, 44035 Nantes Cedex, France

Received 2 February 1996; Revised 10 July 1996; Accepted 10 July 1996

HASCOËT, M. AND M. BOURIN. *Anticonflict effect of alpidem as compared with the benzodiazepine alprazolam in rats.* PHARMACOL BIOCHEM BEHAV **56**(2) 317–324, 1997.—A comparative study between two drugs acting on the $GABA_A$ receptor, alprazolam and alpidem was undertaken, using simple tests such as measurement of spontaneous locomotor activity, four plates test and rotarod in mice. Additional conflict test was further performed using a new conflict paradigm where the opportunity existed for rats to choose during punished periods between immediate, punished reinforcement and delayed non-punished reinforcement. The benzodiazepine alprazolam, demonstrated, as expected, strong anxiolytic effects in mice and increased punished response in rats at non sedative doses (0.5, 1 mg/kg). High doses of alprazolam decreased spontaneous locomotor activity and induced myorelaxant effects in mice. Alpidem, an imidazopyridine derivative, induced motor impairment in mice and only very weak anxiolytic effects in the four plates test in mice (4 mg/kg) and in punished procedure in rats (32 mg/kg). As alprazolam is a full agonist for the $GABA_A$ receptor complex and alpidem is a partial agonist acting with specificity on ω1 $GABA_A$ receptor subtypes, the results are discussed. Activity on ω1 receptor subtypes is perhaps not sufficient in order to obtain a true anti-conflict effect and compounds such as alpidem only relieve some of the symptoms of anxiety disorders.

Alpidem Alprazolam Conflict paradigm Mice Rats $GABA_A$ receptor complex

THE DISCOVERY and increasing knowledge of the macromolecular $GABA_A$ receptor complex, has stimulated the development of new molecules with chemical structures unrelated to benzodiazepines (e.g. β-carbolines, cyclopyrrolones, triazolopyridazines and imidazopyridine) (17). The effects of these compounds and of the benzodiazepines are mediated through ω modulatory sites (20). These modulatory sites appear to require the presence of α, ω,and γ subunit proteins, where the pharmacology is largely dependent on the α subunit present (α_1,.....α_6) (9,27,28,32). According to these findings, benzodiazepine receptors have now been classified as ω modulatory sites (ω receptors). Drugs that act preferentially at a specific w modulatory site may produce only some of the pharmacological effects mediated through the $GABA_A$ receptor complex, such as anxiolysis, muscle relaxation, anticonvulsant and sedative effects. It is therefore of great interest to develop anxiolytic drugs of new chemical structure possessing potential benefits over the benzodiazepines (BZDs). One such approach is to develop compounds which act at certain subtypes of benzodiazepine receptors. It has been established that most of the benzodiazepines do not discriminate between ω_1 and ω_2 modulatory sites.

Alpidem (ALPI) is an imidazopyridine derivative which binds selectively and with high affinity to the ω_1 receptor subtype (11). In addition, ALPI displays low intrinsic activity (43) and thus is classified as a partial agonist for benzodiazepine receptors. Partial agonists induce smaller responses than do full agonists (16) and require a higher receptor occupancy for a given effect (2). Full agonists manifest their effects at relatively low occupancy, while some partial agonists may not manifest full agonist effects even at 100% occupancy (24). Consequently, the combined effects of receptor selectivity and low intrinsic activity of ALPI may produce specific pharmacological actions with less side effects than the benzodiazepines.

[1] Request for reprints should be addressed to: M. Bourin, laboratoire de Pharmacologie et GIS médicament, Faculty of Medicine, University of Nantes, 1 rue Gaston Veil, 44035 Nantes Cedex, France, Telephone: (33) 40-41-28-53, Facsimile: (33) 40-41-28-56.

Specific actions such as anxiolysis are expected without sedation, memory impairment and development of tolerance. Considerable research is now focused on the search for drugs which are anxioselective.

Using a new conflict procedure (18), Hascoët et al (1994) have demonstrated strong anticonflict effects of diazepam in comparison with new anxiolytic compounds such as the azapirones. The present experiment, using the same conflict procedure in rats (18) was performed to examine the potential anxiolytic effects of ALPI in comparison with alprazolam (ALPRA), a triazolobenzodiazepine. In addition, the aim of the study was also to see if a behavioral test, such as the anticonflict procedure, can discriminate between the anxiolytic profile of the drug and the subtype specificity. Another point was that this conflict procedure not only determined the potential anxiolytic profile of the drug, but also tried to examine the animals capacity to wait for reward (37). Additional preliminary tests in mice, such as actimeter, rotarod and four plates test were performed with both drugs.

MATERIALS AND METHODS

The ethical rules of the French Ministry of agriculture for experiments with laboratory animals (N° 87.848) were followed at all times.

PRELIMINARY STUDIES IN MICE

Subjects

Male mice (Swiss strain, 4 weeks old) purchased from R. Janvier (Le Genest) were used. Their average body weight on the day of study was 22 g ± 2 g. These animals were housed in groups of 20, at constant room temperature (20°C) with lights on between 0700h and 1900h, and had free access to food and water.

Drugs

ALPRA, (Upjohn Pharmaceutical, 0.03 to 4 mg/kg) and ALPI (Synthelabo, 0.25 to 16 mg/kg) were injected in a 5% solution of Tween 80. Drugs or vehicle were administered intraperitoneally (IP) in a volume of 0.5 ml/20g body weight. Animals were used only once for each test used.

Psychopharmacological Tests

Actimeter test. The spontaneous activity of animals was recorded using a photoelectric actimeter (6). This apparatus consists of transparent cages in which the animal's activity is measured by light beams connected to a photoelectric cell. The activity is recorded during a 10 min test period.

The "four plates" test. This apparatus consists of a cage floored by four metal plates connected to a device that can generate electric shocks (0.6 mAmps, 0.5 s). Following a 15 s latency period, the animal is subjected to an electric shock after crossing from one plate to another. The number of crossings is recorded during a 1 min test period (3).

The rotarod test. This test evaluates changes in motor function induced by myorelaxation. The naive animal is placed on a rod which rotates at a constant speed (12 revolutions per min). The number of falls is observed over a period of 3 min (12).

Analysis of Data

The mean number of responses for each group and for each test was calculated and the final results were expressed as percentage ± SEM (standard error of the mean) of the value observed in control animals or as mean ± SEM (see the text). Statistical analysis of the data was performed by application of the non parametric Kruskall–Wallis test for independent groups, followed by the Newman–Keuls test. All analyses were conducted using the PCSM program (Deltasoft) for IBM compatible computer.

CONFLICT PARADIGM IN RATS

Subjects

The experiments were carried out on 56 adult male Wistar rats weighing 100g at the beginning of training and 250–300g at the time of the test sessions. "Animals from Le Centre d'élevage R. Janvier, France" arrived in the laboratory at least one week before the experiments. They were housed 4 per cage in standard conditions, at a room temperature of 22° ± 1°C. Rats were maintained at approximately 80% of their initial free feeding body weight throughout the experiment by providing a limited amount of standard rodent diet after each experimental session. Tap water was freely available in the home cage. Rats were subjected to daily IP saline injections over a period of 1 week before receiving drugs. Testing sessions were carried out Monday to Friday, between 8am and 1pm for 5 months.

Drugs

ALPI (4 to 32 mg/kg) and ALPRA (0.06 to 2 mg/kg) were injected in a 5% solution of Tween 80. Drugs or vehicle were administered IP in a volume of 0.5 ml/100g body weight.

Apparatus

Animals were tested in standard rodent operant test chambers (Campden Instruments Ltd) placed in ventilated, sound-attenuated cubicles. One wall of the chamber contained a recess into which a dispenser could deliver 45 mg food pellets. Two apertures were situated 5 cm above and 2.5 cm on either side of the recess. A motor-driven retractable lever could be inserted into the chamber through each aperture. The chamber was supplied with four lights (3 W, 24 V each); one situated above each lever, one above the food hopper, and one in the middle of the ceiling (house light). Each chamber was fitted with a grid floor. Electric shocks (0.4 mA, 45ms) could be delivered to each grid by a shock generator and scrambler.

Training Procedure

This model has been described by Hascoët et al (1994)(18). Rats were subjected daily to a 17 min training session. During all sessions the house light was present in the chamber. Rats were trained to press the two levers with both levers continuously present in the chamber. The schedule of reinforcement was raised progressively over a 15-day period from a fixed ratio (FR1, each press reinforced by a pellet) to an FR8 schedule (i.e. one pellet after 8 presses) of food presentation. Thereafter animals underwent the final conflict training procedure.

For conflict training, each daily session was organised in five successive periods totalling 17 min (alternating between punished and non punished periods) as follows: periods 1, 3 and 5, (3 min), were non punished with only the right lever being presented. As in the training sessions, food was presented on a FR8 schedule of reinforcement. During periods 2 and 4, the conflict periods, (4 min) a foot shock was presented (punishment). The punishment periods were signalled by illu-

mination of the cue light above the food hopper and the insertion of the second lever (left side). This lever operated on a FR8 schedule of reinforcement, while during this period, each press of the right lever was now reinforced by one pellet according to a FR1 schedule and associated with a foot shock. That is, the animal was now presented with a choice of responding.

When stable baselines of responding were obtained (i.e. rats obtained a stable total performance), which required an average of approximately 3 weeks after initiation of final training schedule conditions, drug studies were initiated.

Testing Sessions

Drug studies were carried out using the same procedure as described in the conflict training session. All drugs were administered 30 min prior to training. Drug treatments were administered no more frequently than at 7-day intervals. Rats were randomly assigned to a treatment group.

Results and Statistics

The final results were expressed as the mean number of lever presses ± SEM ($n = 8$). For the drug effect study each rat served as its own control. The mean number of lever presses across the final 2 days of the conflict training for each rat was used as the control value. Thus, drugs were used as the within-subject factor for statistical analysis. The different parameters assessed were: (a) the total performance of rats during the entire test session, (b) the number of punished and (c) non punished responses during conflict periods and (d) the total number of responses during the non conflict periods.

Data were evaluated by nonparametric methods, as they were not normally distributed. Two kinds of analysis were performed: 1) a comparison of drug effects with the control group (within subject factor) were obtained by means of Wilcoxon's signed rank test for paired data ($p \leq 0.05$*, $p \leq 0.01$**); and 2) the drug dose effects with doses as the between-subject factor, were analysed by the Kruskall–Wallis "H" test for independent groups. Additional Newman–Keuls *a posteriori* tests were applied to the data, when appropriate, to detect differences between groups ($p \leq 0.057$•, $p \leq 0.01$••).

All statistical work was carried out using P.C.S.M. program (Deltasoft) for the IBM compatible microcomputer.

RESULTS

Behavioral Studies in Mice

Actimeter test. ALPRA administration resulted in a biphasic effect. The drug increased activity at lower doses (0.03 and 0.06 mg/kg, $p \leq 0.05$* and $p \leq 0.01$**. For a dose of 0.5 mg/kg ($p \leq 0.01$*) and higher doses, ALPRA produced severe motor impairment. ALPI significantly altered spontaneous activity in mice for doses from 8 mg/kg ($p \leq 0.05$*, for 8 and 16 mg/kg respectively and $p \leq 0.01$** for 32 mg/kg) (Tables 1 and 2).

Four plates test. ALPRA increased punished crossing from a dose of 0.25 mg/kg and remained active at higher doses with a peak activity at 0.5 mg/kg ($p \leq 0.01$**).The effect of ALPI in this test was weak, with only the dose of 4 mg/kg significantly increasing punished crossings ($p \leq 0.05$*) (Tables 1 and 2).

Rotarod test. ALPRA produced marked myorelaxation ($p \leq 0.05$* for a dose of 0.25 mg/kg). No significant myorelaxant effects were seen in this test with ALPI-treated animals. The increase in the number of falls for higher doses is correlated with sedative doses (Tables 1 and 2).

Conflict Paradigm in Rats

Alprazolam. ALPRA (0.25 to 2 mg/kg IP) elicited, as expected, a dose-dependent significant increase in punished responding during the conflict periods ($p \leq 0.01$**), with the maximum effect at 1 mg/kg (26 ± 10.30 punished responses versus 2 ± 0.32 for controls) (Fig. 1). However, ALPRA also markedly depressed unpunished responding at higher doses (1 and 2 mg/kg, respectively 55%, $p \leq 0.01$** and 16% of

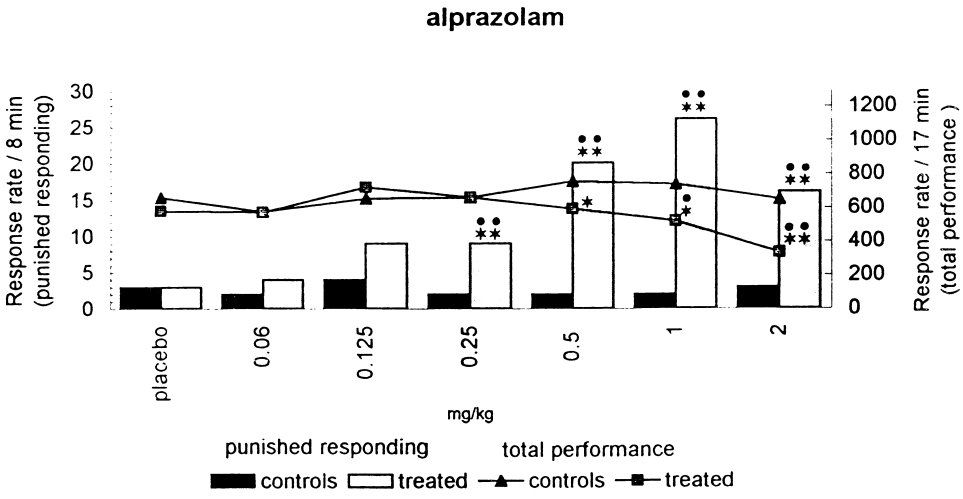

FIG. 1. Effects of alprazolam injected IP, 30 min before the test, on the number of shocks received (punished responding) (Histograms) and on the total performance of rats (curves). The data represent the means of 8 rats for each group. Treated groups were compared with control values by use of the Wilcoxon test for paired groups, $p \leq 0.05$*, $p \leq 0.01$**. Drugs effects were also compared to control vehicle with the Kruskall–Wallis test, followed by the Newman–Keuls *a posteriori* test when appropriate, $p \leq 0.05$•, $p \leq 0.01$••.

TABLE 1
ALPRAZOLAM

Doses mg/kg	0	0.03	0.06	0.125	0.25	0.5	1	2	4
Spontaneous activity	153 ± 15	204 ± 13*	230 ± 14**	187 ± 17	118 ± 10	67 ± 11**	31 ± 7**	19 ± 3**	37 ± 7**
Four plates test	6 ± 0.5	6.4 ± 0.5	6.8 ± 0.6	6.6 ± 0.6	8.3 ± 0.5**	11 ± 0.5**	9.2 ± 0.6**	8.3 ± 0.7*	8 ± 1
Rotarod test	1.3 ± 0.3	1 ± 0.4	0.7 ± 0.3	2 ± 0.5	4.3 ± 0.7	17 ± 2.3**	—	—	—

activity, $p \leqslant 0.01$**). The decrease in unpunished responses was more marked during periods 2 and 4 (both levers present) than during periods 1, 3 and 5 (Tables 3 and 4)

Alpidem. Doses of 4, 8 and 16 mg/kg of ALPI failed to significantly increase the punished response during periods 2 and 4 (Fig 2). ALPI (32 mg/kg) weakly increased punished responses, with a magnitude less than that of the other compounds tested (4 ± 1.47 punished responses versus 0.58 ± 0.16 for control animals $p \leqslant 0.05$*). Furthermore, ALPI decreased total performance at higher doses with a maximum effect at the dose of 32 mg/kg (445 ± 160 unpunished responses versus 1090 ± 40 for controls, $p \leqslant 0.01$**).

DISCUSSION

Several animal models are available for determining anxiolytic-like activity of benzodiazepines (36,38,39). One benefit of the present model over classical conflict models using operant behavior is the choice of escape from punishment by active behavior such as pressing the nonpunished associated lever. In this model, diazepam was found to dramatically increase punished responding associated with high reinforcement, even though the animal had the opportunity to avoid punishment by pressing the lever for delayed reinforcement (18). In comparison with diazepam, ALPRA, in the present study, showed a better separation between sedative effects and anxiolytic-like effects. The increase of punished response during the conflict period was more important. ALPRA shows a different profile of action from the 1,4-benzodiazepines. In addition to the anxiolytic effect, it demonstrates antidepressant-like activity in animals (25) and in humans (1,30). Several authors (8,23,34,35) have also found ALPRA to be efficacious in the treatment of panic disorders. Pentylenetetrazole is used to decrease $GABA_A$ receptor activity and the administration of this drug before the shock-induced-suppression of drinking in thirsty rats (Vogel's conflict test paradigm) emphasised the punished behavioral suppression. In such a procedure, it was found that the potencies and efficacies of the anti-panic benzodiazepines, including ALPRA, surpassed those of the anxiolytic BZDs such as diazepam and ALPI (13). They explained that this kind of action might be due to specific binding to a particular subtype of $GABA_A$ receptors. Lopez et al (1988) (22) have already suggested that ALPRA has an unusual binding that may explain the increase in motor activity at lower doses (7). This effect was not found with the traditional 1,4-benzodiazepine diazepam (18).

The other drug tested in our paradigm, ALPI, was withdrawn from clinical use because of liver toxicity. However, it can be a useful tool with which to understand the pharmacology and therapeutic profile of ω_1 partial agonists (11,20).

ALPI dramatically decreased the spontaneous motility of mice at the dose of 8 mg/kg. The literature is confusing with regard to the sedative effects. ALPI has been demonstrated to induce very little sedation in animals (43), some people have reported that sedative effects are only seen at high doses (4), however, ALPI produces less drowsiness than diazepam in humans (29). Conflicting data have also been reported concerning myorelaxant effects, with an increase in the number of falls during the rotarod test session in our study and no relaxation reported by Dimsdale et al (1988) (11) using the same test. In this study, the data obtained with ALPI in the rotarod test could only be the results of sedative effects in regards to actimeter test. ALPI was not very active in either test of anxiolytic activity, i.e. the conflict test or four plates test. This finding is in agreement with the results of Jones et al (1994) (19) who demonstrated that ALPI has very little effect in the four plates test or the elevated plus maze in mice.

In our conflict test ALPI demonstrated very weak activity, and only at one dose (32 mg/kg), with a magnitude that cannot be compared with the benzodiazepines. Furthermore, it decreased unpunished responses by 50%. Zivkovic et al (1990) (43) and Sanger et al (1993) (31) reported similar results in lever pressing for a food reward procedure in rats, however ALPI produced an anti-punishment effect in a shock-induced suppression of drinking paradigm. Nevertheless, this effect was 10 times less potent than that of diazepam and 3 times less than that of chlordiazepoxide. Analysis of the receptor

TABLE 2
ALPIDEM

Doses mg/kg	0	0.25	0.5	1	2	4	8	16	32
Spontaneous activity	115 ± 13	—	—	108 ± 12	92 ± 16	75 ± 9*	44 ± 9*	37 ± 10**	22 ± 11**
Four plates test	5 ± 0.3	4.1 ± 0.6	4.1 ± 0.4	4.8 ± 0.5	4.6 ± 0.6	7 ± 0.7*	5.2 ± 0.5	—	—
Rotarod test	0.2 ± 0.1	0.8 ± 0.4	1 ± 0.3	0.9 ± 0.3	0.7 ± 0.3	1.9 ± 0.5	2.6 ± 1.2	—	—

TABLE 3

EFFECTS OF DRUGS DURING NON CONFLICT PERIOD

mg/kg	Saline Controls	0.06	0.125	0.25	0.5	1	2	4	8	16	32
Alprazolam					*•	*••	**••				
Treated	330 ± 33	304 ± 59	413 ± 51	383 ± 74	322 ± 21	276 ± 36	201 ± 50	—	—	—	—
Controls	358 ± 26	312 ± 41	367 ± 35	347 ± 68	355 ± 29	375 ±35	357 ± 56	—	—	—	—
Alpidem									**•	**•	*•
Treated	—	—	—	—	—	—	—	423 ± 38	215 ± 43	242 ± 71	198 ± 27
Controls	—	—	—	—	—	—	—	487 ± 9	442 ± 17	622 ± 25	515 ± 27

The data represent the mean number of lever presses ± SEM (n = 8). "—" non tested doses. Treated groups were compared with control values by use of the Wilcoxon test, for paired group; ($p \leqslant 0.05$*, $p \leqslant 0.01$**, within subject analysis). Drug dose effects were also compared to saline control (ALPRA) or lowest dose (ALPI) with the Kruskall–Wallis test, followed by the Newman–Keuls a posteriori test when appropriate; ($p \leqslant 0.05$•, $p \leqslant 0.01$••, between subjects analysis).

TABLE 4

EFFECTS OF DRUGS UPON UNPPUNISHED RESPONSES, DURING CONFLICT PERIOD (PERIODS 2 AND 4)

mg/kg	Saline Controls	0.06	0.125	0.25	0.5	1	2	4	8	16	32
Alprazolam					**•	**•	**••				
Treated	253 ± 26	267 ± 48	303 ± 51	269 ± 69	249 ± 44	219 ± 65	117 ± 50	—	—	—	—
Controls	304 ± 38	293 ± 45	285 ± 47	313 ± 60	398 ± 52	380 ± 58	290 ± 65	—	—	—	—
Alpidem										**•	**•
Treated	—	—	—	—	—	—	—	377 ± 53	257 ± 58	239 ± 72	198 ± 74
Controls	—	—	—	—	—	—	—	424 ± 17	378 ± 13	634 ± 28	515 ± 27

The data represent the mean number of lever presses ± SEM (n = 8). "—" non tested doses. Treated groups were compared with control values by use of the Wilcoxon test, for paired group; ($p \leqslant 0.05$*, $p \leqslant 0.01$**, within subject analysis). Drug dose effects were also compared to saline control (ALPRA) or lowest dose (ALPI) with the Kruskall–Wallis test, followed by the Newman–Keuls *a posteriori* test when appropriate; ($p \leqslant 0.05$•, $p \leqslant 0.01$••, between subjects analysis).

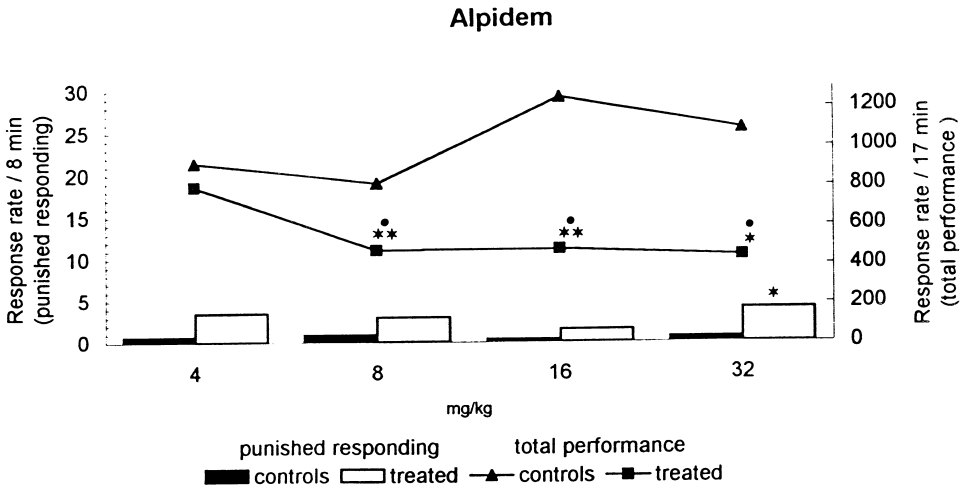

FIG. 2. Effects of alpidem injected IP, 30 min before the test, on the number of shocks received (punished responding) (Histograms) and on the total performance of rats (curves). The data represent the means of 8 rats for each group. Treated groups were compared with control values by use of the Wilcoxon test for paired groups, $p \leq 0.05$*, $p \leq 0.01$**. Drugs effects were also compared to control vehicle with the Kruskall–Wallis test, followed by the Newman–Keuls *a posteriori* test when appropriate, $p \leq 0.05$•, $p \leq 0.01$••.

occupancy revealed that ALPI has strong sedative effects on spontaneous behaviour at very low receptor occupancies in mice (15%) so that any possible anxiolytic activity cannot be efficacious (19). In comparison, ALPRA exhibited anxiolytic-like effects at about 20% of receptor occupancy in the four plate test and 45% in the elevated plus maze test. An 80% of receptor occupancy must be reached to obtain sedative effects (19).

In addition to partial or full agonist activity involved in anti-conflict activity, it is possible that the difference might be explained by the binding of the drugs to particular subtypes of the $GABA_A$ receptor subunit. The imidazopyridine ALPI exhibited high selectivity for the ω_1 receptor subtype and a lesser selectivity for the ω_3 receptor subtype. The affinity of ALPI for the ω_3 receptor in rat tissues is very high (21). An interesting question is whether or not the profile of ALPI is related to its specificity at the ω_1 site, containing an a1 subunit. Sedative effects might result from the stimulation of ω_1 receptors (10). Perrault et al (1988) (26) also reported that the hypnoselective properties of zolpidem may be linked to its selectivity for ω_1 sites and that those sites would be responsible for the sedative effect of the benzodiazepines. Moreover, low myorelaxant potential seems to be linked to the low affinity of ALPI for ω_2 receptors (5).The ω_2 receptor subtype could be responsible for myorelaxant, anxiolytic and anticonvulsivant effects. The increase in the number of falls observed in the rotarod test in our study could be indicative of sedative effects rather than myorelaxant effects. The involvement of ω_3 receptors in anxiety disorders is still uncertain, but it has been demonstrated that the density of the ω_3 receptor is reduced in anxious patients (40). It is therefore possible that the weak effect of ALPI seen in our conflict paradigm could be attributed to a lack of binding to some subtypes of the $GABA_A$ receptor complex. In a recent study (15), Griebel et al reported that the weaker efficacy of ω_1 selective agents might be related to their lack of activity at certain w receptors. ALPRA has been found to be more efficacious on $GABA_A$ receptor subtypes containing α_1, β_1, γ_2 or α_5, β_1, γ_2 subunits (13). A significant proportion of receptor subtypes containing the α_5 subunit have been found in the hippocampus (40,42). This brain structure has been implicated in anxiety disorders and in the brain behavioural inhibition system (14). Stephens and Voet (1994) (33) hypothesised that the α_5-containing isoform of the $GABA_A$ receptor complex could play a role in the behavioral inhibition system. This is an important point to consider as we have first demonstrated that the present paradigm was not only a conflict model but also reduces the capacity to tolerate delays in reward (18). It is important to consider the added variable of impulsivity and this model has been shown, using diazepam and alprazolam, to be extremely sensitive to benzodiazepines. Our results are in agreement with those of Thiébot et al (1985)(37), who reported, using a T-maze paradigm, rats treated with benzodiazepines showed a reduction in tolerance to delays in reward, indicating a reduction in impulse control. The lack of a definitive effect of ALPI in this model might be also due to negligible activity on impulsivity control.

Whatever the effect of ALPI as a partial agonist, or towards subtype selectivity, the results have shown weak activity in a punished paradigm without being free of sedative effects. The difference with classical benzodiazepines may be related with preferential sedative properties of ω_1 compounds, and it has been hypothesised that anxiolysis was observed at doses that decreased locomotor activity (15). Activity on ω_1 receptor subtypes is perhaps not sufficient in order to obtain true anti-conflict effects and compounds such as alpidem only relieve some of the symptoms of anxiety disorders.

ACKNOWLEDGEMENT

The authors thank Glen Baker for helping them in order to improve the writing of the manuscript.

REFERENCES

1. Ansseau, M.; Ansoms, C.; Beckers, G.; Bogaerts, M.; Botte, L.; De Buck, R.; Diricq, S.; Dumortier, A.; Jansegers, E.; Owieczka, J.; and Stellamans, G. Double blind clinical study comparing alprazolam and doxepin in primary unipolar depression. J. Affect. Disord. 7:287–296; 1984.
2. Ariëns, E. J.; Simoni, A.M. A molecular basis for drug action. J. Pharm. Pharmacol. 16:137–141; 1964.
3. Aron, C.; Simon, P.; Larousse, C.; Boissier, J. M. Evaluation of a rapid technique detecting minor tanquilizers. Neuropharmacology 10:459–469; 1971.
4. Bassi, S.; Albizzati, M.; Ferrarese, C.; Frattola, L.; Cesana, B.; Piolti, R.; Farolfi, A. Alpidem, a novel anxiolytic drug. A double-blind placebo controlled study in anxious outpatients. Clin. Neuropharmacol. 12:67–74; 1989.
5. Benavides, J.; Peny, B.; Ruano, D.; Vitorica, J.; Scatton, B. Comparative autoradiographic distribution of central (benzodiazepine) modulatory site subtypes with high, intermediate and low affinity for zolpidem and alpidem. Brain Res. 604:240–250; 1993.
6. Boissier, J. R.; Simon, P. Action de la caféine sur la motilité spontanée de la souris. Arch. Int. Pharmacodyn. 158:212–221; 1965.
7. Bourin, M.; Hascoët, M.; Mansouri, B.; Colombel, M.C.; Bradwejn, J. Comparison of behavioral effects after single and repeated administrations of four benzodiazepines in three mice behavioral models. J. Psychiatr. Neurosc., 17:72–77; 1992.
8. Chouinard, C.; Annable L; Fontaine R and Solyom L. Alprazolam in the treatment of generallized anxiety and panic disorders: A double-blind, placebo-controlled study. Psychopharmacology. 77: 229–233; 1982.
9. De Lorey, T.M.; Olsen, R.W. γ-Aminobutyric acid$_A$ receptor structure and function. J Biol Chem 267:16747–50; 1992.
10. Depoortere, H.; Zivkovic, B.; Lloyd, K. G.; Sanger, D.; Perrault, G.; Langer, S. Z.; Bartholini, G. J. Zolpidem, a novel nonbenzodiazepine hypnotic. I. Neuropharmacological and behavioral effects. Pharmacol. Exp. Ther. 237:649–658; 1986.
11. Dimsdale, M.; Friedmann, J. C.; Morselli, P. L.; Zivkovic, B. Alpidem. Drugs of the future 13:106–109; 1988.
12. Dunham, N. W.; Mya, T. S. A note on a simple apparatus for detecting neurological deficit in rats and mice. J. Am. Pharm. Assoc. 46:208–209; 1957.
13. Giusti, P.; Guidetti, G.; Costa, E.; Guidotti, A. The preferential antagonism of pentylenetetrazole proconflict responses differentiates a class of anxiolytic benzodiazepines with potential antipanic action. J. Pharmacol. Exp. Ther. 257:1062–1068; 1991.
14. Gray, J. A. Issues in the neuropsychology of anxiety. In Tuma AH, Maser JD (eds); ''Anxiety and the Anxiety Disorders'' Hillside, NJ: Lawrence Erlbaum, pp. 5–26; 1985.
15. Griebel, G.; Sanger, D. J.; Perrault, G. The use of the rat elevated plus maze to discriminate between non selective and BZ-1 (ω_1) selective, benzodiazepine receptor ligands. Psychopharmacology. 124:245–254; 1996.
16. Haefely, W.; Martin, J. R.; Schoch, P. Novel anxiolytics acting as partial agonists at benzodiazepine receptors. Trends Pharmacol. Sci. 11:452–456; 1990.
17. Hascoët, M.; Couëtoux du Tertre, A.; Le Melledo, J. -M.; Bourin, M. Les récepteurs GABA$_A$ centraux: structure, mécanisme d'action et implications cliniques. Inf. Psychiatrique 10:949–959; 1993.
18. Hascoët, M.; Bourin, M.; Todd, K. G.; Couëtoux du Tertre, A. Anti-conflict effect of 5-HT$_{1A}$ agonists in rats: A new model for evaluating anxiolytic-like activity. J. Psychopharmacol. 8:227–237; 1994.
19. Jones, G. H.; Schneider, C.; Schneider, H. H.; Seidler, J.; Cole, B. J.; Stephens, D. N. Comparison of several benzodiazepine receptor ligands in two models of anxiolytic activity in the mouse: An analysis based on fractional receptor occupancies. Psychopharmacology 114:191–199; 1994.
20. Langer, S. Z.; Arbilla, S. Imidazopyridines as a tool for the characterisation of benzodiazepine receptors: A proposal for a pharmacological classification as omega receptors subtypes. Biochem Behav. 29:763–766; 1988.
21. Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. Zolpidem and Alpidem: Two imidazopyridines with selectivity for 1 and 3 receptor subtypes. GABA and benzodiazepine receptor subtypes, (eds. by G. Biggio and E. Costa). Raven Press, New York: 61–72; 1990.
22. Lopez, F.; Miller, L. G.; Greenblatt, D. J.; Paul, S. M.; Shader, R. I. Low-dose alprazolam augments motor activity in mice. Pharmacol. Biochem. Behav. 30:511–513; 1988.
23. Lydiard R.B.; Lesser M.; Ballenger J.C.; Rubin R.T.; Laraia M. and Dupont R. A fixed dose study of alprazolam 2 mg, alprazolam 6 mg, and placebo in panic disorder. J. Clin. Psychopharmacol. 12:96–103; 1992.
24. Malizia, A. L.; Coupland, N. J.; Nutt, D. J. Benzodiazepine Receptor Function In Anxiety Disorders. in: GABA$_A$ Receptors and Anxiety: From Neurobiology to Treatment (eds. by G. Biggio, E. Sanna, M. Serra and E. Costa). Raven Press, New York 115–133; 1995.
25. O' Connor, W. T.; Earley, B.; Leonard, B. E. Antidepressant properties of the triazolobenzodiazepines alprazolam and adinazolam: Studies of the olfactory bulbectomised rat model of depression. Br. J. Clin. Pharmacol. 19:45–56; 1985.
26. Perrault, G.; Morel, E.; Sanger, D. J.; Zivkovic, B. The interaction between zolpidem and β-CMC: A clue to the identification of receptor sites involved in the sedative effect of zolpidem. Eur. J. Pharmacol. 156:189–196; 1988.
27. Pritchett; D. B.; Seeburg, P. H. γ-Aminobutyric acid$_A$ receptor α_5-subunit creates novel type II benzodiazepine receptor pharmacology. J. Neurochem., 54:1802–1804; 1990.
28. Pritchett, D. B.; Lüddens, H.; Seeburg, P. H. Type I and type II GABA$_A$ benzodiazepine receptors produced in transfected cells. Science, 245:1389–1392; 1989.
29. Reignier, F.; Chastel, A.; L'Heritier, C.; Magni, G.; Henry, M. Comparaison en double aveugle contre placebo de l'alpidem en dose unique (50 mg ou 75 mg) dans un modèle d'anxiété situationnelle. Thérapie 44:279–283; 1989.
30. Rickels, K.; Feighner, J. P.; Smith, W.T. Alprazolam, amitriptyline, doxepin and placebo in the treatment of depression. Arch. Gen. Psychiatry. 42:134–141; 1985.
31. Sanger, D. J.; Perrault, G.; Morel, E.; Joly, D.; Zivkovic, B. The psychopharmacological profile of alpidem. In Imidazopyridines in anxiety disorders (eds Bartholini, G.; Garreau, M.; Morselli, P. L.; Zivkovic, B.) Raven Press, New York, 73–84; 1993.
32. Schofield, P. R.; Darlison, M. G.; Fujita, N.; Burt, D. R.; Stephenson, F. A.; Rodriguez, H.; Rhee, L. M.; Ramachandran, J.; Reale, V.; Glencorse, T. A.; Seeburg, P. H.; Barnard, E. A. Sequence and functional expression of the GABA$_A$ receptor shows a ligand-gated receptor super-family. Nature. 328:221–227; 1987.
33. Stephens, D. N.; Voet, B. Differential effects of anxiolytic and non-anxiolytic benzodiazepine receptor ligands on performance of a differential reinforcement of low rate (DRL) schedule. Behav. Pharmacol., 5:4–14; 1994.
34. Tesar, G. E. High-potency benzodiazepines for a short-term management of panic disorder: The US experience. J. Clin. Psychiat. 51:[Suppl]4–10; 1990a.
35. Tesar, G. E. Diagnosis and treatment of panic disorders. J. Med. 57:61–66; 1990b.
36. Thiébot, M. H.; Soubrié, P. Behavioral Pharmacology of the Benzodiazepines. in: The Benzodiazepines From Molecular Biology to Clinical Practice, (ed. by E. Costa). Raven Press, New York. 67–91; 1983.
37. Thiébot, M. H.; Le Bihan, C.; Soubrié, P.; Simon, P. Benzodiazepines reduce the tolerance to reward delay in rats. Psychopharmacology. 86:147–152;1985.
38. Treit, D. Animal models for the study of anti-anxiety agents: A review. Neurosci Biobehav Rev. 9:203–222; 1985.
39. Treit, D. Anxiolytic effects of benzodiazepines and 5HT$_{1a}$ agonists: Animal models. In 5HT$_{1a}$ agonists, 5HT$_3$ antagonists and benzodiazepines: Ttheir comparative behavioral pharmacology. (eds: Rodgers, R. J. and Cooper, S. J.) J. Wiley & Son Ltd. 31–57;1991.
40. Turner, J. D.; Bodewitz, G.; Thompson, C. L.; Stephenson, F. A.

Immunohistochemical mapping of $GABA_A$ receptor alpha subunits in rat CNS. In:Anxiolytic β-Carbolines: From molecular biology to the clinic (Ed. DN Stephens),.Springer Verlag, Heidelberg; 29–49; 1993.
41. Weizmann, R.; Tanne, Z.; Granek, M.; Karp, L.; Golomb, M.; Tyano, S.; Gavish, M. Peripheral benzodiazepine binding sites on platelet membranes are increased during diazepam treatment of anxious patients. Eur. J. Pharmacol., 138:289–292; 1987.
42. Wisden, W.; Laurie, D. J.; Monyer, H.; Seeburg, P. H. The distribution of 13 $GABA_A$ receptor subunit mRNAs in the rat brain. I. Telecephalon, diencephalon, mesoencephalon. J. Neurosc., 12: 1040–1062; 1992.
43. Zivkovic, B.; Morel, E.; Joly, D.; Perrault, G.; Sanger, D. J.; Lloyd, K. G. Pharmacological and behavioral profile of alpidem as an anxiolytic. Pharmacopsychiatry 23 [suppl]:108–113; 1990.