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Differences in Anxiolytic-Like Profile of Two Novel Nonbenzodiazepine BZ (ω) Receptor Agonists on Defensive Behaviors of Mice

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GRIEBEL, G., G. PERRAULT AND D. J. SANGER. *Differences in anxiolytic-like profile of two novel nonbenzodiazepine BZ (ω) receptor agonists on defensive behaviors of mice.* PHARMACOL BIOCHEM BEHAV **62**(4) 689–694, 1999.—The present experiments compared the behavioral effects of two novel BZ (ω) receptor agonists, the pyridazinone Y-23684 (1–30 mg/kg) and the pyrido[1,2-a]benzimidazole RWJ-46771 (0.01–0.3 mg/kg) with the BZs diazepam (0.5–3 mg/kg) and clobazam (1–30 mg/kg) in the mouse defense test battery (MDTB), a model for the screening of anxiolytic drugs. In the MDTB, Swiss mice were confronted with a natural threat (a rat) and situations associated with this threat. Primary measures taken during and after rat confrontation were flight, risk assessment, defensive threat/attack, and escape attempts. Results showed that clobazam and Y-23684 significantly modified all defense responses in the presence of the rat at doses that did not decrease spontaneous locomotor activity. These drugs decreased avoidance reactions after the rat was introduced into the runway, reduced flight speed and risk assessment activities of mice chased by the rat, increased risk assessment displayed when subjects were constrained in a straight alley, and reduced defensive threat and attack behaviors upon forced contact. Diazepam significantly decreased all but one (number of avoidances when the rat was first introduced into the runway) defensive behaviors. RWJ-46771 reduced risk assessment in the chase test, avoidance responses, flight speed, and defensive threat and attack reactions, but these effects occurred in the great part at motor-impairing doses, suggesting that the decrease in defensiveness may have been contaminated by behavioral suppression. Finally, following the removal of the rat from the runway, only Y-23684 reduced escape behavior at doses that did not decrease spontaneous behavior. Taken together, these findings demonstrate that Y-23684 displayed anxiolytic-like activity comparable to that of BZs in the MDTB. Although RWJ-46771 significantly modified most defensive behaviors, the effects may have been confounded by decreases in locomotor activity.

Benzodiazepines Diazepam Clobazam Y-23684 RWJ-46771 Anxiety Defensive behavior Flight Risk assessment Swiss mouse

EVEN though benzodiazepines (BZs) are relatively safe drugs, and are widely used in the treatment of anxiety, insomnia, and epilepsy, they may produce untoward side effects such as muscle relaxation, memory impairment, tolerance, and physical dependence (19). The search for positive modulators of BZ (ω) receptors with more specific therapeutic action without the concomitant unwanted effects has led to the development of new BZs that show different efficacies at BZ (ω) receptors (i.e., bretazenil, imidazenil) (6,21) or compounds chemically unrelated to BZs that selectively bind to specific BZ (ω) receptor subtypes (i.e., zolpidem and abecarnil) (5,20,23). For example, studies in animals showed that the nonselective BZ (ω) receptor partial agonist imidazenil displayed comparable or even greater efficacy in anxiety models than BZs but was less effective than the latter in tests of ataxia and muscle relaxation or coordination (6,15).

In the search for novel anxiolytic agents devoid of undesirable side effects, several BZ (ω) receptor agonists, structurally unrelated to BZs, have been synthesised. It has been shown that the pyridazinone derivative and selective partial agonist at BZ (ω) receptors (K_i = 41 nM; IC_{50} > 10,000 nM at $GABA_A$, dopamine D_2, noradrenaline α_{1-2}, 5-HT_{1A}, 5-HT_2, and muscarine receptors) Y-23684 displayed an anxiolytic-like profile in rodents over a wide dose range in a variety of

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procedures including conflict tests (Geller-Seifter and punished drinking tests) and exploration models (elevated plus-maze and light/dark tests) in the absence of effects on spontaneous motor activity (24). The pyrido[1,2-a]benzimidazole derivative RWJ-46771, which binds with subnanomolar affinity (IC_{50} = 0.42 nM) to the BZ site of the $GABA_A$ receptor, has been shown to display potent anticonflict activity in the punished drinking test (22). The compound has been described as partial agonist (22).

The present study was undertaken to investigate further the anxiolytic-like potential of Y-23684 and RWJ-46771 in an experimental procedure designed for screening anxiety-modulating agents in mice, namely the Mouse Defense test Battery (MDTB) (10). Effects were compared with those of the clinically effective anxiolytic BZs diazepam and clobazam. The MDTB elicits and measures reactions to both present and anticipated threat (i.e., a rat). In this model, Swiss mice show an extremely precise delineation of defensive behaviors including flight, risk assessment, defensive threat/attack, and escape attempts, with each behavior controlled by specifiable characteristics of the threat stimulus and situation. Extensive pharmacological investigations have demonstrated that the MDTB is a useful tool for evaluating potential anxiolytics (10–12,16).

METHOD

Animals

Subjects were naive male Swiss mice aged 10 weeks at the time of testing, and male Long–Evans rats (400–500 g). They were obtained from Iffa-Credo (L'Arbresle, France). Prior to experimental testing, they were housed singly in standard cages (mice: 30 × 20 × 14 cm; rats: 44 × 30 × 20 cm) containing a constant supply of food pellets and water. All animals were maintained under standard laboratory conditions (22–23°C; relative humidity: 45–82%) and kept on a 12 L:12 D cycle with light onset at 0600 h. All animal housing and experimental methods were in accordance with current French legislation on animal experimentation.

Drugs

Diazepam, clobazam, RWJ-46771 (2-Fluorophenyl-pyrido [1,2]benzimidazole) (synthesized by the Chemistry Department, Synthélabo Recherche), and Y-23684 [(±)-2-(4-chlorophenyl)- 5,6-dihydro-benzothiepino-[5,4-c]pyridazin-3(2H)-one 7-oxide] (Yoshitomi Pharmaceutical Industries, Japan) were prepared as suspensions in physiological saline containing one or two drops of Tween 80. All doses are expressed as the bases and were chosen on the basis of previous results with these compounds in behavioral studies (22,24).

Apparatus

The test was conducted in an oval runway, 0.40 m wide, 0.30 m high, and 4.4 m in total length, consisting of two 2-m straight segments joined by two 0.4-m curved segments and separated by a median wall (2.0 × 0.30 × 0.06). The apparatus was elevated to a height of 0.80 m from the floor to enable the experimenter to easily hold the rat, while minimizing the mouse's visual contact with him. All parts of the apparatus were made of black Plexiglas. The floor was marked every 20 cm to facilitate distance measurement. Activity was recorded with video cameras mounted above the apparatus. The room illumination was provided by one red neon tube fixed on the ceiling and two desk lamps with red bulbs placed respectively on two tables (elevated to a height of 1 m) located 1 m away from the runway. The light intensity in the runway was 7 lx. Experiments were performed under red light between 0930 and 1500 h. The experimenter was unaware of the drug treatment.

Procedure

Effects on spontaneous locomotor activity: The pretest. Subjects were placed into the runway for a 3-min familiarization period during which line crossings were recorded.

The rat avoidance test. Immediately after the 3-min familiarization period, a hand-held dead rat (killed by CO_2 inhalation) was introduced into the runway and brought up to the subject at a speed of approximately 0.5 m/s. Approach was terminated when contact with the subject was made or the subject ran away from the approaching rat. If the subject fled, avoidance distance (the distance from the rat to the subject at the point of flight) was recorded. This was repeated five times. Mean avoidance distance (cm) was calculated for each subject. The results were expressed as mean avoidance distance and mean number of avoidances.

The chase test. The hand-held rat was brought up to the subject at a speed of approximately 2.0 m/s. During the chase, flight speed (measured when the subject is running straight), number of stops (pause in movement), orientations (subject stops, then orients the head toward the rat), and reversals (subject stops, then runs in the opposite direction).

The straight alley test. After the chase was completed, the runway was then converted to a straight alley by closing a door at one end. During 30 s, the hand-held rat remained at a constant distance of 40 cm from the subject and the number of approaches followed by withdrawals (subject must move more than 20 cm forward from the closed door, then return to it) were recorded. The hand-held rat remained at the place it was introduced during the full 30 s. After this session, it was removed from the straight alley area.

The forced contact test. Finally, the experimenter brought the rat up to contact the subject. For each such contact the following defensive threat and attack reactions were noted: vocalizations, upright postures, and bites by the subjects. This was repeated three times. The results were expressed as mean number of vocalizations, upright postures, and bites.

The contextual defense test. Immediately after the forced contact test, the rat was removed and the door was opened. Escape attempts including wall rears, wall climbs, and jump escapes were recorded during a 3-min session. See Griebel et al. (17) for additional details on this test battery.

Statistical Analysis

Data were analyzed by a one-way analysis of variance (ANOVA). Subsequent comparisons between treatment groups and control were carried out using Dunnett's *t*-test.

RESULTS

Effects on Spontaneous Locomotor Activity: The Pretest

Table 1 shows that prior to confrontation with the rat, clobazam, $F(4, 45) = 9.91$, $p < 0.001$, and RWJ-46771, $F(4, 45) = 8.88$, $p < 0.001$, but not the other drugs, significantly decreased the number of line crossings.

Effects on Flight

This behavior includes the measures from the avoidance test and flight speed. Table 2 shows that the avoidance dis-

TABLE 1

LOCOMOTOR ACTIVITY IN THE RUNWAY CAGE BEFORE THE CONFRONTATION WITH THE RAT

	Dose (mg/kg, IP)	Line Crossings
Diazepam	0	127.6 ± 9.6
	0.5	138.6 ± 16.1
	1	139.5 ± 22.0
	3	95.1 ± 13.7
Clobazam	0	139.4 ± 6.8
	1	131.3 ± 7.0
	3	141.5 ± 7.8
	10	108.8 ± 6.1*
	30	79.8 ± 12.2*
Y-23684	0	125.7 ± 10.5
	1	108.8 ± 16.8
	3	166.5 ± 26.0
	10	119.2 ± 10.2
	30	125.3 ± 12.7
RWJ-46771	0	146.8 ± 9.9
	0.01	120.0 ± 11.0
	0.03	102.4 ± 8.7*
	0.1	74.6 ± 16.0*
	0.3	57.9 ± 12.4*

Y-23684 was administered 60 min before the beginning of the test. The other drugs were injected 30 min before the test. Data represent mean ± SEM.

$n = 6$–10.

*$p < 0.05$ (Dunnett's t-test).

TABLE 2

EFFECTS OF TWO CLASSICAL AND TWO NOVEL BENZODIAZEPINE RECEPTOR LIGANDS ON THREE FLIGHT MEASURES IN THE MOUSE DEFENSE TEST BATTERY

	Dose (mg/kg, IP)	Avoidance Distance (cm)	Number of Avoidance	Flight Speed (m/s)
Diazepam	0	160.6 ± 7.3	3.6 ± 0.4	0.9 ± 0.1
	0.5	126.4 ± 12.5*	2.9 ± 0.6	0.8 ± 0.1
	1	91.4 ± 8.9*	2.0 ± 0.5	0.7 ± 0.1
	3	76.0 ± 7.7*	2.4 ± 0.4	0.5 ± 0.1*
Clobazam	0	164.3 ± 4.8	4.6 ± 0.2	1.1 ± 0.1
	1	129.0 ± 6.7*	3.6 ± 0.3*	0.9 ± 0.1
	3	117.5 ± 8.1*	3.4 ± 0.3*	0.8 ± 0.1*
	10	72.6 ± 5.5*	1.1 ± 0.4*	0.5 ± 0.1*
	30	80.0 ± 0.0*	0.1 ± 0.1*	0.5 ± 0.1*
Y-23684	0	146.9 ± 7.3	4.0 ± 0.5	0.9 ± 0.1
	1	108.6 ± 20.3	2.8 ± 0.4	0.7 ± 0.1
	3	98.6 ± 18.2	2.2 ± 0.6	0.9 ± 0.1
	10	100.2 ± 12.3	2.7 ± 0.6	0.6 ± 0.1*
	30	62.0 ± 15.9*	1.2 ± 0.4*	0.6 ± 0.1*
RWJ-46771	0	148.1 ± 8.6	4.2 ± 0.3	1.0 ± 0.2
	0.01	126.2 ± 8.0	3.6 ± 0.3	0.7 ± 0.1
	0.03	127.0 ± 9.2	2.7 ± 0.3*	0.7 ± 0.1
	0.1	101.4 ± 13.5*	1.7 ± 0.4*	0.4 ± 0.1*
	0.3	48.0 ± 0.0*	0.3 ± 0.3*	0.4 ± 0.1*

Data represent mean ± SEM.

* $p < 0.05$ (Dunnett's t-test)

tance was significantly modified by diazepam, $F(3, 27) = 16.1$, $p < 0.001$, clobazam, $F(4, 32) = 20.47$, $p < 0.001$, Y-23684, $F(4, 22) = 3.92$, $p < 0.05$, and RWJ-46771, $F(4, 35) = 4.57$, $p < 0.01$. Post hoc analysis indicated that diazepam (from 0.5 to 3 mg/kg), clobazam (from 1 to 30 mg/kg), Y-23684 (30 mg/kg), and RWJ-46771 (0.1 and 0.3 mg/kg) significantly reduced avoidance distance. Clobazam, $F(4, 45) = 45.45$, $p < 0.001$, Y-23684, $F(4, 24) = 4$, $p < 0.05$, RWJ-46771, $F(4, 45) = 20.69$, $p < 0.001$, but not diazepam significantly modified the number of avoidances. This parameter was reduced by clobazam at all doses, by Y-23684 at the highest dose and by RWJ-46771 from 0.03 to 0.3 mg/kg. In the chase test, all drugs significantly affected flight speed: [diazepam: $F(3, 28) = 3.56$, $p < 0.05$; clobazam: $F(4, 45) = 12.79$, $p < 0.001$; Y-23684: $F(4, 24) = 7$, $p < 0.001$; and RWJ-46771: $F(4, 45) = 6.66$, $p < 0.001$. Subsequent analysis showed that the speed was reduced by diazepam at 3 mg/kg, by clobazam from 3 to 30 mg/kg, and by Y-23684 and RWY-46771 at the two highest doses (10–30, and 0.1–0.3 mg/kg, respectively).

Effects on Risk Assessment

This behavior includes stops, orientations, reversals, and approaches/withdrawal responses. Figure 1 shows that all drugs significantly modified risk assessment responses in the chase test. Stops were reduced by diazepam, $F(3, 28) = 14.5$, $p < 0.05$, at 1 and 3 mg/kg, by clobazam, $F(4, 45) = 33.67$, $p < 0.001$, and Y-23684, $F(4, 24) = 20$, $p < 0.001$, at all doses, and by RWJ-46771, $F(4, 45) = 19.03$, $p < 0.001$, from 0.03 to 0.3 mg/kg. Orientations were decreased by diazepam, $F(3, 28) = 9.4$, $p < 0.001$, at 1 and 3 mg/kg, by clobazam, $F(4, 45) = 16.63$, $p < 0.001$, and Y-23684, $F(4, 24) = 8.87$, $p < 0.001$, from 3 to 30 mg/kg, and by RWJ-46771, $F(4, 45) = 21.34$, $p < 0.001$, at all doses. Reversals were reduced by diazepam, $F(3, 28) = 9$, $p < 0.001$, at all doses, by clobazam, $F(4, 45) = 7.99$, $p < 0.001$, from 3 to 30 mg/kg, by Y-23684, $F(4, 24) = 3.45$, $p < 0.05$, and RWJ-46771, $F(4, 45) = 6.66$, $p < 0.01$, at the two highest doses (10–30 and 0.1–0.3 mg/kg, respectively). In the straight alley test, diazepam, $F(3, 28) = 4.63$, $p < 0.01$, clobazam, $F(4, 45) = 8.64$, $p < 0.001$, Y-23684, $F(4, 24) = 2.75$, $p < 0.05$, but not RWJ-46771 significantly modified approaches followed by withdrawal responses. This behavior was increased by diazepam at 3 mg/kg, by clobazam at 10 and 30 mg/kg, and by Y-23684 at 10 mg/kg.

Effects on Defensive Threat/Attack

Figure 2 shows that the drugs significantly modified all defensive threat and attack responses. Bites were reduced by diazepam, $F(3, 28) = 27.96$, $p < 0.001$, Y-23684, $F(4, 24) = 11.1$, $p < 0.001$, and RWJ-46771, $F(4, 45) = 4.53$, $p < 0.001$, at the two highest doses, and by clobazam, $F(4, 45) = 48.95$, $p < 0.001$, at all doses tested. Upright posture was reduced by diazepam, $F(3, 28) = 40.4$, $p < 0.001$, at 3 mg/kg, and by clobazam, $F(4, 45) = 107.71$, $p < 0.001$, Y-23684, $F(4, 24) = 8.84$, $p < 0.001$, and RWJ-46771, $F(4, 45) = 5.96$, $p < 0.001$, at the two highest doses tested. Vocalizations were significantly decreased by diazepam, $F(3, 28) = 23.49$, $p < 0.001$, at 1 and 3 mg/kg, by clobazam, $F(4, 45) = 49.84$, $p < 0.001$, from 3 to 30 mg/kg, by Y-23684, $F(4, 24) = 3.8$, $p < 0.05$, at 10 and 30 mg/kg, and by RWJ-46771, $F(4, 45) = 3.62$, $p < 0.05$, at the highest dose.

Effects on Contextual Defense: The Posttest

Table 3 shows that clobazam, $F(4, 45) = 29.76$, $p < 0.001$, Y-23684, $F(4, 24) = 4.36$, $p < 0.01$, and RWJ-46771, $F(4, 45) = 21.74$, $p < 0.001$, but not diazepam significantly reduced the

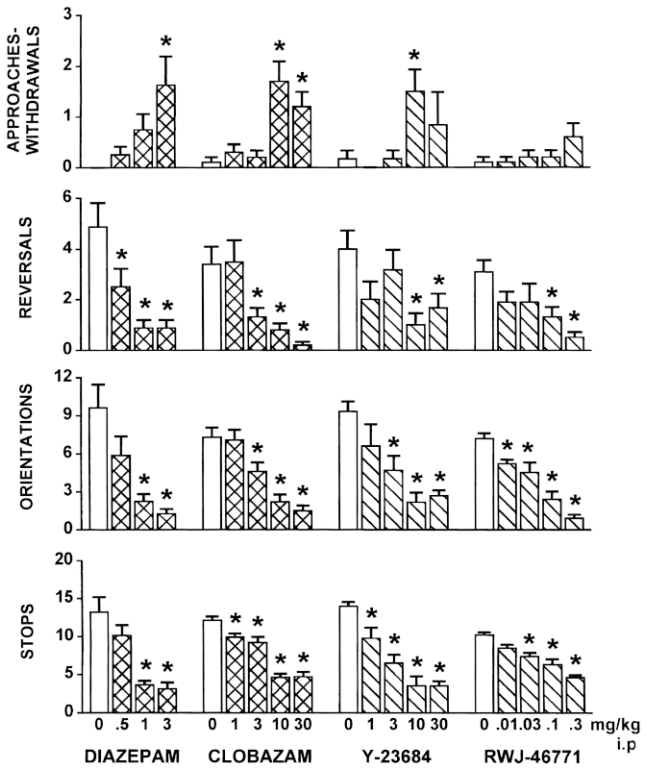

FIG. 1. Effects of two classical and two novel benzodiazepine receptor ligands on risk assessment responses measured during the chase test (reversals, stops, and orientations) and in the straight alley situation (approaches/withdrawals). Data represent mean ± SEM. *$p <$ 0.05 (Dunnett's *t*-test).

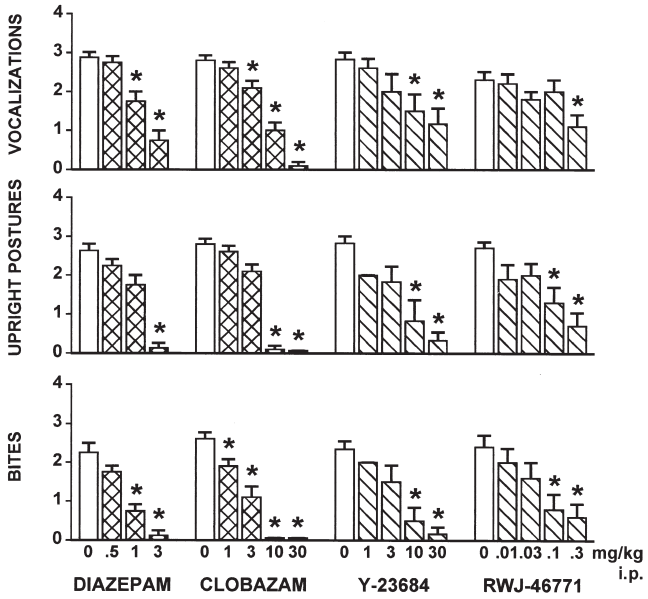

FIG. 2. Effects of two classical and two novel benzodiazepine receptor ligands on defensive threat and attack reactions upon forced contact with a dead Long–Evans rat. Data represent mean ± SEM. *$p <$ 0.05 (Dunnett's *t*-test).

number of escape attempts following the removal of the rat from the runway apparatus. Statistical significance was reached by clobazam and RWJ-46771 at the two highest doses (10–30 and 0.1–0.3 mg/kg, respectively), and by Y-23684 at 30 mg/kg.

DISCUSSION

The present findings show that the two novel BZ (ω) receptor agonists Y-23684 and RWJ-46771, modulate defensive reactions of Swiss mice confronted with a rat stimulus or situations associated with this threat.

Whereas clobazam, Y-23684 and RWJ-46771 decreased all flight responses, diazepam only partially affected this behavior as it reduced avoidance distance after the rat was first introduced into the runway and flight speed during the chase test, but failed to significantly modify the number of avoidances. Although this latter profile contrasts somewhat with that obtained with diazepam in a previous study, where the drug failed to alter avoidance distance and flight speed, but significantly reduced the number of avoidances (16), it confirms further the idea that classical BZs (e.g., chlordiazepoxide, clorazepate) may have variable effects on flight behavior (2). The effects of diazepam, clobazam, and Y-23684 are unrelated to motor impairment as data from the pretest indicated that these drugs did not modify spontaneous motor activity at the doses that affected flight. In contrast, RWJ-46771 (0.1 and 0.3 mg/kg) reduced flight at doses that also reduced line crossings, suggesting that these effects may have been contaminated by behavioral suppression. The extensive pharmacological evaluation of the MDTB has demonstrated that panic-modulating compounds specifically affect animals' flight responses with panicogenic treatment (e.g., yohimbine) increasing flight, and antipanic drug challenge (e.g., clonazepam, alprazolam, imipramine, fluoxetine, moclobemide, phenelzine) decreasing it (3,8,13,14,16). Notably, these studies showed that avoidance distance appears to be particularly sensitive to panic-modulating drug treatment. In view of the clinical efficacy of clobazam in the management of panic disorder [e.g., (18)], the flight-reducing action of the drug provides further evidence that this defense response may be of particular interest in the study of the neural mechanisms underlying panic attacks. In addition, the results obtained with Y-23684 and RWJ-46771 on flight suggest that the former may possess potency as a therapeutic agent for panic disorder, while RWJ-46771 may have a very limited potential as in this respect.

During the chase test, diazepam, clobazam, and Y-23684 reduced risk assessment activities (i.e., stops, orientations, and reversals), whereas in the straight alley situation, they increased risk assessment behavior (i.e., approaches followed by withdrawals displayed when subjects were constrained in one part of the runway). Although RWJ-46771 decreased orientations at all dose levels, it modified stops and reversals only at motor-impairing doses. Moreover, the drug failed to modify risk assessment in the straight alley.

Risk assessment consists of various information-gathering activities that occur primarily in the context of uncertainty concerning the threat characteristics of the stimulus (1). Because of a potential isomorphism between risk assessment activities and certain key features of GAD (e.g., hypervigilance, apprehensive expectation, and scanning), it has been suggested that they may represent a pattern of responses particularly sensitive to anxiolytic drug challenge (1). This was subse-

TABLE 3
EFFECTS OF TWO CLASSICAL AND TWO NOVEL BENZODIAZEPINE RECEPTOR LIGANDS ON ESCAPE ATTEMPTS FROM THE RUNWAY APPARATUS AFTER THE REMOVAL OF THE RAT IN THE MOUSE DEFENSE TEST BATTERY

	Dose (mg/kg)	Escape Attempts
Diazepam	0	30.6 ± 10.8
	0.5	27.3 ± 9.6
	1	24.5 ± 8.7
	3	19.0 ± 6.7
Clobazam	0	44.9 ± 14.2
	1	40.1 ± 12.7
	3	34.2 ± 10.8
	10	7.7 ± 2.4*
	30	3.9 ± 1.2*
Y-23684	0	29.2 ± 11.9
	1	30.4 ± 13.6
	3	25.8 ± 10.6
	10	21.8 ± 8.9
	30	11.5 ± 4.7*
RWJ-46771	0	43.7 ± 13.8
	0.01	34.3 ± 10.9
	0.03	32.9 ± 10.4
	0.1	13.4 ± 4.2*
	0.3	3.1 ± 1.0*

Data represent mean ± SEM.
*$p < 0.05$ (Dunnett's t-test).

quently confirmed by extensive pharmacological investigations showing that BZs affected these responses (4,10,16). Thus, the actions of Y-23684 and RWJ-46771 may be consistent with an anxiolytic-like effect. However, the finding that RWJ-46771 modified these risk assessment measures mostly at motor-impairing doses indicates only partial efficacy in affecting these behaviors, and therefore, suggests that this drug may have a weaker anxiety-reducing potential compared to classical anxiolytics.

When contact was forced between threat stimulus and subject, diazepam, clobazam, Y-23684, and RWJ-46771 markedly reduced vocalizations, upright postures, and bites to the rat. Nevertheless, RWJ-46771 decreased these behaviors at motor-impairing doses only, suggesting that the reduction in defensive reactions upon forced contact with the rat may have been confounded by behavioral suppression. The profile of diazepam, clobazam, and Y-23684 is very similar to that observed in previous studies with classical (i.e., BZs) and atypical (i.e., 5-HT_{1A} receptor agonists and 5-HT reuptake inhibitors) anxiolytics in the MDTB, thereby confirming that these terminal defense reactions are reliable indices of anxiety (7, 10,12,16). This was subsequently confirmed by a factor analysis showing that defensive threat/attack loaded on a factor probably related to anxiety (9). In addition, this study revealed that, unlike risk assessment, which includes cognitive aspects of defensive behaviors, defensive threat, and attack behaviors reflect a more "affective"-orientated defense. Whether this may indicate that RWJ-46771 would be of limited utility in anxiety states where affective-oriented symptoms are the main feature remains to be established.

Following the removal of the rat from the runway, only Y-23684 specifically decreased escape attempts from the test apparatus. Marked reductions in these behaviors during the postrat period have been observed with 5-HT_{1A} receptor ligands (10,12,16), whereas 5-HT/NA reuptake inhibitors weakly decreased them (7).

In summary, the behavioral profile displayed by two novel BZ (ω) receptor agonists in this study showed that Y-23684 produced clear anxiolytic-like activity in the MDTB, whereas RWJ-46771 had either nonspecific or weak anxiolytic-like effects. The results obtained with Y-23684 confirm previous findings showing that this drug was very effective in different models of anxiety. Y-23684 increased punished responding in the Geller-Seifter and the water-lick conflict tests, increased exploratory behavior of the aversive areas in the elevated plus-maze and the light/dark tests, and increased social interaction behavior. All these effects occurred over a wide dose range (i.e., 5–50 mg/kg PO, in the conflict tests; 0.1–10 mg/kg PO in the other tests) in the absence of effects on motor coordination (24). In contrast, the nonspecific anxiolytic-like action of RWJ-46771, which has been described as a partial agonist, is somewhat unexpected. However, in in vitro experiments, RWJ-46771 produced a GABA shift value [1.6, from which one can assess the intrinsic activity for BZ (ω) receptor ligands] somewhat greater than that observed with BZ (ω) receptor partial agonists (i.e., 1.0) and close to that of the BZ (ω) receptor full agonist lorazepam (i.e., 1.7) (22). As a result, we would expect RWJ-46771 to behave as a full agonist in behavioral studies (e.g., impairing locomotor activity at doses close to those producing anxiolytic-like effects).

In conclusion, the results of the present study showed that the pyrido[1,2-a]benzimidazole derivative RWJ-46771 reduced defensive reactions of mice confronted with a natural threat or a situation associated with this threat only at doses that also impaired spontaneous locomotor activity. In contrast, the pyridazinone Y-23684 produced clear effects on defensive behaviors over a wide dose range without impairing spontaneous motor activity, thereby suggesting that it may possess a potential utility for the treatment of anxiety disorders without the depressant effects seen with classical BZs.

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