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ORIGINAL INVESTIGATION

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Behavioural profiles of the reversible monoamine-oxidase-A inhibitors befloxatone and moclobemide in an experimental model for screening anxiolytic and anti-panic drugs

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Abstract The present study compared the behavioural effects of acute and chronic (one daily IP injection for 14 days) treatments with the reversible monoamine oxidase-A inhibitors (RIMAs) moclobemide (3 and 10 mg/kg) and befloxatone (0.3 and 1 mg/kg) in the Mouse Defence Test Battery (MDTB) which has been designed for screening anxiolytic and anti-panic drugs. In the MDTB, Swiss mice were confronted with a natural threat (a rat) and situations associated with this threat. Primary measures taken before, during and after rat confrontation were escape attempts, flight, risk assessment (RA) and defensive threat and attack. After acute administration of both compounds, no modification of defensive behaviours were observed. This was in contrast to chronic treatments, where moclobemide (3 and 10 mg/kg) and befloxatone (1 mg/kg) produced a significant reduction in one flight measure (avoidance distance when the rat was approaching). In addition, befloxatone (0.3 and 1 mg/kg), but not moclobemide, increased RA responses when mice were constrained in one part of the apparatus facing the rat, which remained at a constant distance. No other drug effects were observed with either compound. Although these behavioural profiles are consistent with an anxiolytic-like effect, the finding of an action upon a limited number of defence responses suggests a weaker anxiolytic-like potential compared to that of classical anxiolytics. However, in view of previous data with panic-modulating compounds on flight behaviours in the MDTB, the present results are in line with clinical results showing that moclobemide is effective in panic disorders and suggest that befloxatone may have some efficacy in the clinical management of panic.

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Introduction

The reversible inhibitors of monoamine oxidase (RIMAs) were recently introduced into therapy to minimize the risk of serious adverse reactions (e.g. hypertensive crises) associated with the irreversible MAOIs. Clinical trials have shown that these drugs are effective antidepressants with milder side effects than the irreversible inhibitors (Finberg 1995; Priest et al. 1995). In addition, RIMAs have also been found to be useful in other psychiatric disorders involving anxiety, such as panic disorder and social phobia (Liebowitz et al. 1990; Buller 1995; Priest et al. 1995).

Despite the clinical efficacy of RIMAs in some anxiety disorders, there is little evidence that these compounds have anxiolytic-like effects in experimental models of anxiety. To the best of our knowledge, only Caille and colleagues have demonstrated that moclobemide and befloxatone, a novel RIMA which pertains to the oxazolidinone series (Curet et al. 1996), exhibit anxiolytic-like activity in the rat elevated plus-maze test (Caille et al. 1996). The reason for this is unclear, but it is possible that classical animal models of anxiety are insensitive to the action of these compounds. Most of these tests have been pharmacologically validated by benzodiazepines (BZs), which represent the first-choice treatment in generalized anxiety disorders (GAD), and it is not clear whether these models are useful when testing compounds effective in other anxiety disorders. Recently, several novel test procedures have been described as models of anxiety disorders other than GAD, such as obsessive-compulsive disorder (Yadin

et al. 1991; Olivier 1992; Rapoport 1992; Rapoport et al. 1992; Altemus et al. 1993), post-traumatic stress disorder (Servatius et al. 1995) and panic disorder (Fontana and Commissaris 1988; Fontana et al. 1989; Graeff 1991; Hendrie and Neill 1991; Martin 1993; Jenck et al. 1995; Molewijk et al. 1995; Griebel et al. 1996b). For example, it was demonstrated that rat-elicited flight responses in Swiss mice may serve as an experimental model for the screening of panic-modulating compounds as it meets criteria for face validity and predictive validity, normally applied to such models (Griebel et al. 1996b). This test is based on the work of Blanchard and colleagues (1993) on antipredator defence in rats. These authors designed two test batteries, a Fear/Defence Test Battery (F/DTB) measuring defensive behaviours to present, approaching predators (i.e. a cat), and an Anxiety/Defence Test Battery (A/DTB) measuring reactions to potential threat. The recently developed Mouse Defence Test Battery (MDTB) combines many of the features of the F/DTB and the A/DTB into a single procedure, eliciting and measuring reactions to both present (i.e. a rat) and anticipated threat (Griebel et al. 1995b). In a mouse-scaled oval runway, Swiss mice show a precise delineation of defensive behaviours including flight, risk assessment (RA), escape attempts, and defensive threat/attack, with each behaviour controlled by specifiable characteristics of the threat stimulus and situation. Pharmacological studies demonstrated that flight responses elicited by the presentation of a rat are specifically reduced by compounds used in the clinical management of panic such as imipramine, fluoxetine and the BZs alprazolam and clonazepam (Griebel et al. 1996b,c). Other BZs such as chlordiazepoxide, diazepam and clorazepate generally failed to affect flight responses. However, these compounds reduced RA, defensive threat/attack reactions and escape attempts, thereby suggesting that these defence responses may be particularly sensitive to anti-GAD agents. On the basis of these drug findings it was suggested that the MDTB may be useful for the screening of both anti-panic and anti-GAD drugs (Griebel et al. 1995c, 1996b). In the present study, the MDTB was used to examine effects of acute and repeated administration of the two RIMAs moclobemide and befloxatone.

Materials and methods

All procedures described here are in compliance with ethical principles and guidelines for scientific experiments on animals.

Animals

Subjects were naive male Swiss mice aged 9 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 a standard cage (mice: $30 \times 20 \times 14$ cm; rats: $44 \times 30 \times 20$ cm) containing a constant supply of food pellets and water. All animals were maintained under standard laboratory conditions (22–23°C; relative humidity: 40–65%) and kept on a 12-h light/dark cycle with light onset at 6 a.m.

Drugs

Moclobemide and befloxatone (both synthesized by the chemistry department, Synthélabo Recherche) were prepared as suspensions in physiological saline containing 1 or 2 drops of Tween 80. Mice were randomly assigned to treatment with moclobemide (3 or 10 mg/kg; $n = 10$), befloxatone (0.3 or 1 mg/kg; $n = 10$) or saline ($n = 64$) for 14 days administered IP once daily. Twenty-four hours after the last injection mice from the saline group were divided into five treatment groups. They were injected either with saline ($n = 24$), moclobemide (3 or 10 mg/kg; $n = 10$) or befloxatone (0.3 or 1 mg/kg; $n = 10$). Animals chronically treated with moclobemide and befloxatone were injected with moclobemide or befloxatone, respectively. The last injection was performed at day 15, 30 min before testing was carried out. All doses are expressed as the bases and were chosen on the basis of previous results with these compounds in behavioural studies (Caille et al. 1996).

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 ($2.0 \times 0.30 \times 0.06$). 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. In addition, the apparatus was equipped with infrared beams and sensors capable of measuring the velocity of the animal during the chase/flight test. Experiments were performed under red light between 9.30 a.m. and 3 p.m.

Procedure

Effects on spontaneous locomotor activity: the pre-test (*min 1–3*)

Subjects were placed into the runway for a 3-min familiarization period during which line crossings, wall rears, wall climbs, and jump escapes were recorded.

Effects on flight responses: the rat avoidance test (*min 4–6*)

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.

Effects on RA: the chase (min 7–8) and the straight alley (min 9–11) tests

The hand-held rat was brought up to the subject at a speed of approximately 2.0 m/s. During the chase, the number of stops (pause in movement) was recorded. 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/withdrawals (subject must move more than 0.2 m forward from the closed door, then return to it) were recorded. Both responses are described as RA activities (Griebel et al. 1995b).

Effects on defensive threat/attack responses: the forced contact test (min 12–13)

Finally, the experimenter brought the rat up to contact the subject. For each such contact, bites and vocalizations by the subjects were noted. This was repeated three times. The results were expressed as mean number of bites and mean number of vocalizations.

Effects on contextual defence: the post-test (min 14–16)

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. (1996d) for additional details on this test battery.

Statistical analysis

Data were analysed by a one-way analysis of variance (ANOVA) (line crossings, wall rearings, avoidance distance, stops and approaches/withdrawals) or the nonparametric Kruskal-Wallis test for some infrequently occurring or highly variable behaviors (number of avoidances, bites and vocalizations). Subsequent comparisons between treatment groups and control were carried out using Newman-Keuls procedures or the nonparametric Mann-Whitney *U*-test. Pre- versus post-test differences in escape attempts were evaluated by a Friedman ANOVA followed by the Wilcoxon matched pairs test.

Results

Effects on spontaneous locomotor activity: the pre-test

Table 1 shows that neither line crossings [moclobemide: $F(4,47) = 1.71$; befloxatone: $F(4,47) = 1.51$] nor wall rearings [moclobemide: $F(4,47) = 0.66$; befloxatone: $F(4,47) = 2.12$] were significantly modified by any of the drug treatments.

Effects on flight responses: the rat avoidance test

Figure 1 shows that the drugs significantly modified the avoidance distance [moclobemide: $F(4,44) = 2.96$, $P < 0.05$; befloxatone: $F(4,44) = 3.37$, $P < 0.05$], whereas the number of avoidances remained unchanged (moclobemide: K = 1.02; befloxatone: K = 6.98). Post-hoc analysis indicated that chronic treatments with moclobemide (3 and 10 mg/kg) and befloxatone (1 mg/kg) significantly reduced avoidance distance.

Effects on RA

Chase test

Figure 2 shows that none of the drug treatments significantly affected the number of stops during the chase [moclobemide: $F(4,47) = 0.32$; befloxatone: $F(4,47) = 0.95$].

Straight alley test

ANOVA revealed that befloxatone [$F(4,47) = 3.2$, $P < 0.05$], but not moclobemide significantly modified the number of approaches/withdrawals. Post-hoc analysis revealed that befloxatone (0.3 and 1 mg/kg) given repeatedly increased the number of approaches/withdrawal responses.

Effects on defensive threat/attack responses: the forced contact test

Table 2 shows that all drug treatments failed to affect bitings to the rat (moclobemide: K = 2.23; befloxatone: K = 2.31) and vocalizations (moclobemide: K = 0.44; befloxatone: K = 1.1).

Table 1 Locomotor activity in the runway cage before the confrontation with the rat. Drugs were administered IP once a day for 2 weeks (chronic). The last injection was given 30 min before the beginning of the test (acute). Data represent mean ± SEM

Treatments	Line crossings	Wall rearings
Befloxatone (mg/kg)		
Chronic (saline) + acute (saline)	114.33 ± 7.41	7.17 ± 1.35
Chronic (saline) + acute (0.3)	142.30 ± 15.16	12.60 ± 2.03
Chronic (saline) + acute (1)	133.40 ± 8.37	8.40 ± 1.33
Chronic (0.3) + acute (0.3)	122.50 ± 11.16	12.80 ± 1.62
Chronic (1) + acute (1)	111.10 ± 10.07	8.80 ± 2.48
Moclobemide (mg/kg)		
Chronic (saline) + acute (saline)	128.33 ± 11.23	10.58 ± 1.86
Chronic (saline) + acute (3)	140.00 ± 8.02	7.10 ± 1.49
Chronic (saline) + acute (10)	105.60 ± 9.67	10.00 ± 2.55
Chronic (3) + acute (3)	128.40 ± 10.97	9.40 ± 1.13
Chronic (10) + acute (10)	116.00 ± 8.52	11.40 ± 2.49

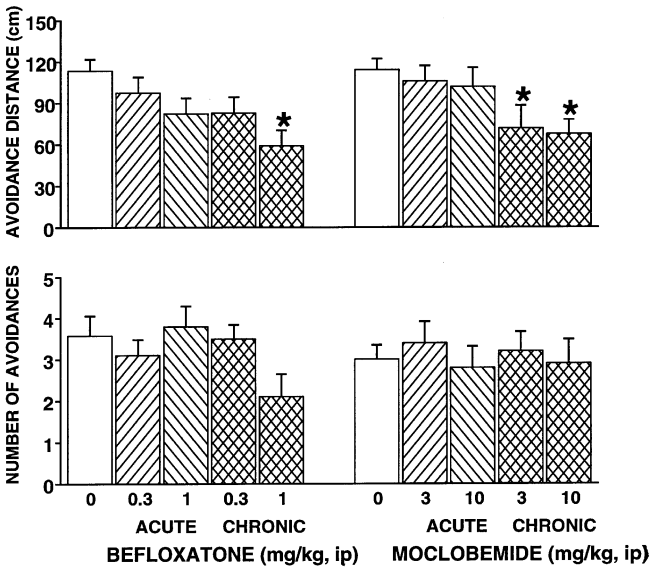

Fig. 1 Effects of acute and chronic (one daily IP injection for 14 days) treatments with moclobemide and befloxatone on two flight measures in the mouse defence test battery. Data represent mean ± SEM. $^*P < 0.05$ (Newman-Keuls)

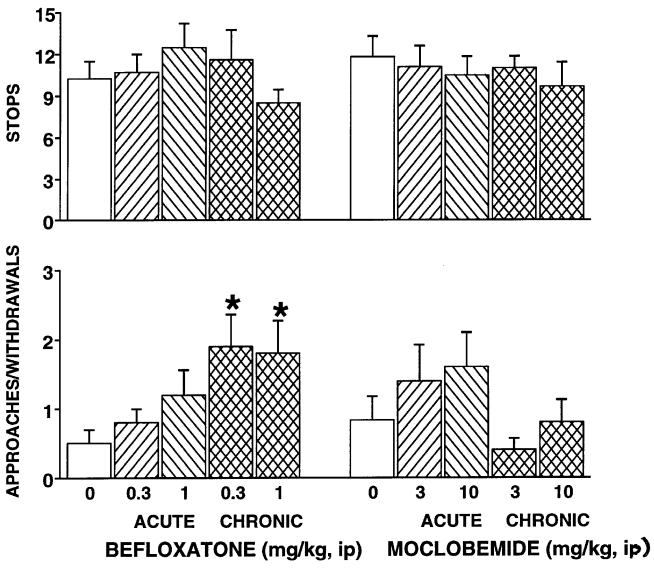

Fig. 2 Effects of acute and chronic treatments with moclobemide and befloxatone on two risk assessment mesures in the mouse defence test battery. Data represent mean ± SEM. $^*P < 0.05$ (Newman-Keuls)

Effects on contextual defence: the post-test

ANOVA indicated a significant drug × test interaction in both experiments [moclobemide: $N(1,52) = 51$, $P < 0.001$; befloxatone $N(1,52) = 48$, $P < 0.001$]. As shown in Fig. 3, escape attempts following the removal of the rat were significantly increased in all groups, but none of the drug treatments inhibited this effect.

Discussion

The present findings show that chronic (15 days), but not acute, administration of the RIMAs moclobemide and befloxatone produced a number of changes in defence responses which may be related to modulation of anxiety and/or panic behaviours. The behavioural profiles of the two RIMAs differ from those seen with BZ anxiolytics and anti-panic drugs observed in earlier studies with the MDTB.

Following acute treatment, neither moclobemide nor befloxatone modified flight reactions after the rat was introduced into the runway. This was in contrast to chronic treatment with both compounds which produced a decrease in one of two flight measures (i.e. avoidance distance). These effects are unrelated to motor impairment, as data from the pre-test indicated that none of the treatments modified spontaneous motor activity. 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 panicolytic drug challenge (e.g. clonazepam, chronic alprazolam, imipramine, fluoxetine) decreasing it (Griebel et al. 1996b,c). Notably, these studies showed that avoidance distance appears to be particularly sensitive to panic-modulating drug

Table 2 Defensive threat and attacks responses of mice confronted with a rat. Drugs were administered IP once a day for 2 weeks (chronic). The last injection was given 30 min before the beginning of the test (acute). Data represent mean ± SEM

Treatments	Vocalizations	Bitings
Befloxatone (mg/kg)		
Chronic (saline) + acute (saline)	3.00 ± 0.00	2.58 ± 0.23
Chronic (saline) + acute (0.3)	2.50 ± 0.34	2.10 ± 0.31
Chronic (saline) + acute (1)	2.90 ± 0.10	2.80 ± 0.20
Chronic (0.3) + acute (0.3)	2.60 ± 0.31	2.20 ± 0.42
Chronic (1) + acute (1)	2.70 ± 0.21	2.40 ± 0.31
Moclobemide (mg/kg)		
Chronic (saline) + acute (saline)	2.92 ± 0.08	2.58 ± 0.19
Chronic (saline) + acute (3)	2.50 ± 0.34	2.10 ± 0.31
Chronic (saline) + acute (10)	2.80 ± 0.13	2.90 ± 0.10
Chronic (3) + acute (3)	2.80 ± 0.20	2.40 ± 0.22
Chronic (10) + acute (10)	2.80 ± 0.20	2.30 ± 0.40

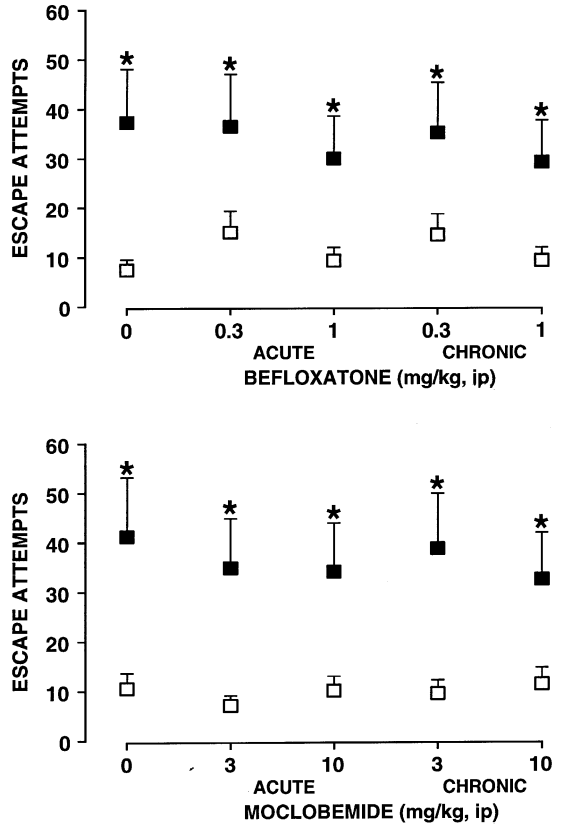

Fig. 3 Effects of acute and chronic treatments with moclobemide and befloxatone on escape attempts following the removal of the rat from the runway apparatus. Data represent mean ± SEM. $^*P < 0.05$ (Wilcoxon matched pairs test). □ Pre-test; ■ post-test

treatment. The present findings with moclobemide are consistent with this idea as two clinical trials demonstrated that the drug significantly improved patients with panic disorder (Berger et al. 1991; Dilbaz and Arihan 1993). Befloxatone is now in clinical development, and no data on its efficacy in panic have been published. On the basis of its effects on flight in the MDTB, we can anticipate potential efficacy of befloxatone in the clinical management of panic. It is interesting to note that earlier findings with the antidepressant drugs imipramine and fluoxetine in the MDTB demonstrated that acute administration of these compounds potentiated flight reactions. These effects were in agreement with the exacerbation in the severity and frequency of panic attacks observed at the beginning of treatment with such agents (Den Boer and Westenberg 1988; Giesecke 1990; Westenberg and Den Boer 1993a,b). The current finding of a lack of potentiation of flight behaviours following single administrations of moclobemide and befloxatone would suggest that these RIMAs, unlike monoamine reuptake inhibitors, do not produce unwanted (i.e. anxiogenic) effects at the initiation of the treatment. Differences in the behavioural profile between RIMAs and the monoamine reuptake inhibitor fluoxetine were recently found by Caille and colleagues, who showed that befloxatone and moclobemide, but not fluoxetine, displayed anxiolytic-like effects in the elevated plus-maze test in rats after a single administration (Caille et al. 1996).

During the chase test, none of the treatments significantly affected RA activities. By contrast, in the straight alley situation, RA was increased by chronic treatment of befloxatone, whereas moclobemide failed to modify this behaviour. RA consists of various information-gathering activities which occur primarily in the context of uncertainty concerning the threat characteristics of the stimulus (Blanchard et al. 1991). Because of a potential isomorphism between RA 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 (Blanchard et al. 1991). This was subsequently confirmed by extensive pharmacological investigations showing that BZs affected these responses (Blanchard et al. 1993; Griebel et al. 1995b). Importantly, in these studies, BZs generally decreased RA in situations where baseline scores were high, whereas they increased RA when control activities were low. Thus, the action of befloxatone on approach/withdrawal responses is consistent with an anxiolytic-like effect. However, the failure of befloxatone to reduce RA during the chase indicates only partial efficacy in affecting these behaviours, and therefore suggests a weaker anxiety-reducing potential compared to classical anxiolytics.

When contact was forced between the rat and the subject, neither acute nor chronic treatments with moclobemide and befloxatone modified defensive threat and attack responses. Earlier findings from the MDTB revealed that classical (e.g. BZs) as well as atypical (e.g. 5-HT reuptake inhibitors, 5-HT_{1A} receptor ligands) anxiolytics reduced bitings and, to a lesser extent, vocalizations, thereby suggesting that these behaviours may be a reliable index of anxiety (Griebel et al. 1995a–d). This was subsequently confirmed by a factor analysis showing that defensive attack responses loaded on a factor probably related to anxiety (Griebel et al. 1996a). In addition, this study revealed that, unlike RA, which includes cognitive aspects of defensive behaviours, defensive attack reflects a more "affective"-orientated defence. Whether this may indicate that moclobemide and befloxatone would be of limited utility in anxiety states where affective-oriented symptoms are the main feature remains to be established. The few clinical trials carried out so far with moclobemide in panic disorder and social phobia provide little relevant information. Clearly, more clinical studies with these compounds in anxiety disorders are required.

Following the removal of the rat from the runway, all drug treatments failed to counteract the potentiation of escape attempts. Marked reductions in these behaviours during the post-rat period have been

observed with BZs (Griebel et al. 1995c,1996c), whereas other anxiolytics either weakly (i.e. 5-HT/NA reuptake inhibitors) (Griebel et al. 1995a) or non-specifically (i.e. at motor-impairing doses) decreased them (e.g. 5-HT_{1A} receptor ligands) (Griebel et al. 1995d). The present findings with moclobemide and befloxatone indicate that inhibition of MAO also may not affect contextual defence, and strengthens the idea that only compounds interacting with the GABA/BZ receptor complex regulate this behaviour.

In summary, the behavioural profiles of moclobemide and befloxatone in the MDTB are consistent with an anxiolytic-like effect. However, the finding of an action on only few defence responses (i.e. on flight and/or RA), either suggests a weaker anxiolytic-like potential compared to BZs or indicates that moclobemide and befloxatone may be effective only in a limited number of anxiety states (e.g. those where panic attacks are the predominant feature). The observation that befloxatone affected flight and RA, whereas moclobemide modified flight only, suggests that befloxatone either may be more effective than moclobemide or may be useful in a broader spectrum of anxiety states compared to the latter compound. In addition, it must be emphasized that, unlike BZs, moclobemide and befloxatone were effective only after chronic treatment. To the best of our knowledge, studies in mice reporting on differences in the magnitude of the inhibition between acute and chronic treatments of befloxatone or moclobemide are lacking. However, in rats microdialysis studies have demonstrated that progressive inhibition of MAO takes place with time following repeated irreversible MAOI or RIMA treatment (for review, see Finberg 1995). This would tend to indicate that a high degree of inhibition is necessary to reduce defensive behaviours.

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