Pharmacology Biochemistry and Behavior, Vol. 65, No. 4, pp. 649–653, 2000

0091-3057/00/$–see front matter

ELSEVIER

PII S0091-3057(99)00237-3

The Anxiolytic-Like Properties of Two Selective MAOIs, Moclobemide and Selegiline, in a Standard and an Enhanced Light/Dark Aversion Test

LUISA DE ANGELIS AND CHIARA FURLAN

Department of Biomedical Sciences, via Giorgeri 7, University of Trieste, Trieste, Italy; and via Durant 10, 34100 Trieste, Italy

Received 11 June 1999; Revised 10 September 1999; Accepted 8 October 1999

DE ANGELIS, L., AND C. FURLAN. *The anxiolytic-like properties of two selective MAOIs, moclobemide and selegiline, in a standard and an enhanced light/dark aversion test.* PHARMACOL BIOCHEM BEHAV **65**(4) 649–653, 2000.— The present study was designed to investigate the putative anxiolytic effects of moclobemide (MOC), a reversible inhibitor of type A monoamine oxidase enzyme (RIMA) antidepressant, in an experimental model of anxiety in mice. The test selected was the light/dark aversion test. In the present investigation, an anxiogenic-like behavior was induced by light, alone as the stimulus (standard version of the test) or by pretreatment with a subconvulsant dose of pentylenetetrazole (PTZ) (15 mg/kg IP) 45 min before testing ("enhanced" version of the test). In mice, the effect of repeated administration for 2 weeks of MOC (0.5, 1, and 5 mg/kg IP) was compared with those of selegiline (SEL) (5, 10, and 20 mg/kg IP), an irreversible and selective MAO-B inhibitor. For comparative purpose, the chronic effect of an established reference anxiolytic, such as lorazepam (LOR) (0.025, 0.05, and 0.10 mg/kg IP), was also evaluated. Results demonstrated that PTZ-treated mice showed a decrease in the number of transitions as well as in the time spent in the lit area, when compared with vehicle controls, an effect characteristic of an anxiogenic response. This anxiogenic-like behavior was reduced by chronic administration of LOR as well as MOC, suggesting an anxiolytic-like effect (as shown in the "standard" version of the test). In addition, the increased aversion of mice for the light compartment of the light/dark box was significantly reduced compared to PTZ-treated mice or vehicle controls. SEL failed to significantly alter the anxiogenic-like behavior induced by subconvulsant doses of PTZ. These data provide additional evidence for the anxiolytic-like effects of MOC administered chronically in the mouse. © 2000 Elsevier Science Inc.

Moclobemide Selegiline Anxiogenic-induced behavior Light-dark aversion test

IN recent years, reversible monoamine oxidase inhibitors (MAOI) antidepressants have been discovered, and have attracted great interest, as these agents appear to reduce the risk of. hypertensive crisis and drug interactions (6). Moclobemide (MOC) is the prototype of reversible inhibitors of type A monoamine oxidase enzyme (RIMAs) (5,13). In addition to being effective in depressive disorders (25), MOC has been shown to be effective in controlled studies for treating panic disorder with agoraphobia (11), social phobia (16), and attention-deficit hyperactivity disorder (26). Furthermore, MOC may improve cognition in conditions associated with cholinergic deficit (29), and in the prophylactic treatment of migraine (20). Recently, it has been used in the treatment of tobacco withdrawal symptoms in smokers (2). However, given the extensive interest at the present time for antidepressant drugs that can used in the treatment of anxiety disorders, especially those in which panic attacks are the major symptom, the purpose of the present study was to assess the putative anxiolytic-like effects of MOC in an experimental model of anxiety.

The test selected was the light/dark aversion test (1). This test is based on the aversive properties of light ("standard"

Requests for reprints should be addressed to Luisa de Angelis, University of Trieste, Department of Biomedical Sciences, via Giorgeri 7, Trieste, Italy.

version), and uses as its index of anxiety the time spent in the lit area as opposed to the time spent in the dark area. In the present investigation, anxiogenic-like behavior was induced by pretreatment with the prototype of anxiogenic drugs, pentylenetetrazole ("enhanced" version of the test) (18). In mice, the chronic effects of MOC were compared with those of selegiline (SEL), an irreversible and selective MAO-B inhibitor (28). For comparison, it was considered of interest to evaluate the effects of chronic treatment with a well-established anxiolytic drug, i.e., lorazepam (LOR).

METHOD

Animals

Female Charles River CD1 mice, aged 60 days and weighing 22–24 g at the time of experimentation, were used. They were housed in groups of 10 in opaque polycarbonate boxes (27 × 21 × 14 cm) under standard laboratory conditions, and maintained on a controlled lighting cycle (dark period 0700–1900 h) for 14 days prior to the beginning of drug administration. A reversed light/dark cycle is critical for exploratory behavior in this model of anxiety, because behavioral changes are affected by plasma corticosterone levels, with the greatest sensitivity occurring during the dark cycle (23).

All testing was performed according to the recommendations and policies of the U.S. National Institute of Health guidelines for the use of laboratory animals.

Drugs

The following drugs and doses were used: lorazapem (TAVOR, Wyeth, Aprilia, Italy): 0.025, 0.05, and 0.10 mg/kg; moclobemide (Roche, Milano, Italy): 0.5, 1, and 5 mg/kg; (−)selegiline hydrochloride (Chiesi Farmaceutici, Parma, Italy): 5, 10, and 20 mg/kg; pentylenetetrazole (Aldrich Chemie, Steinheim, Germany): 15 mg/kg, The doses are expressed in terms of base or salt as indicated above, and were selected on the basis of other preclinical studies or our previous experiments (7,8,22). LOR solutions were prepared by diluting the commercial solutions in distilled water. Appropriate vehicle solutions were used for control injections. In experiments using vehicle administrations, preliminary studies indicated that the response of vehicle-injected and nontreated mice were indistinguishable, and in the following results only the response of vehicle-treated animals is given. All drugs or vehicle were administered intraperitoneally (IP) in a volume of 0.01 ml/g body weight.

Light-Dark Aversion Test

The test was performed according to Belzung et al. (1). The apparatus consisted of two polycarbonate boxes (27 × 21 × 14 cm) with an interconnecting plastic tunnel (7 × 10 cm). One of these boxes was darkened by black paint and covered with a black cover. The other box was lit by a 60-W desk lamp 30 cm above the box, which provided the only laboratory illumination. The apparatus was positioned on a bench 1 meter above the floor.

Procedure

All drugs except PTZ were administered once daily for 14 days. On day 15, an injection of the drug or vehicle was given 30 min before the light/dark aversion test ("standard" version of the test). An increase in anxiogenic-like behavior was induced by pretreatment with subconvulsant doses of PTZ (15 mg/kg IP) 45 min before testing ("enhanced" version of the test). Each mouse was placed into the center of the lit box. During the 5-min test, the number of transitions between the lit and dark area and the time spent in the lit area was determined, minute by minute, by an observer in another room via a closed-circuit TV camera. A mouse was considered to have entered the new area when all four legs were in the area. None of the animals were used on more than one occasion. All tests were run between 0900 and 1200 h in a room shielded from laboratory sounds.

Statistical Analysis

Results are expressed as a mean ± SEM. Data were subjected to three-way ANOVA, supplemented where appropriate by Keul's test.

RESULTS

Effects of Pentylentetrazole Given Acutely and Singly

As indicated in Figs. 1, 2, and 3, animals receiving PTZ 15 mg/kg showed a significantly lower number of transitions (Figs. 1A, 2A, and 3A), as well as significantly less time spent in the lit area (Figs. 1B, 2B, and 3B) than vehicle controls, thus indicating an increase in anxiety-like behavior.

Effects of Lorazepam Given Chronically, Singly, or in Association With Acute Pentylentetrazole

The effects of LOR on the number of transition in the light/dark aversion test are presented in Fig. 1A. Analysis of the data in a three-way ANOVA revealed a main effect of LOR on transitions, $F(7, 08) = 87.000$, $p < 0.01$, a main effect of PTZ, $F(7, 08) = 25.77$, $p < 0.01$, a main effect of dose, $F(4, 98) = 4.96$, $p < 0.01$, and LOR × dose interaction, $F(4, 98) = 4.34$, $p < 0.01$. A significant LOR × PTZ interaction was seen. Further statistical analysis (post hoc Keul's test) indicated that all doses of LOR differed significantly ($p < 0.05$) from PTZ. Mice treated with the association of chronic LOR and acute PTZ showed no significant difference from mice treated with chronic LOR.

Comparison of activity scores with regard to the time parameter (Fig. 1B) indicated a main effect of LOR, $F(7, 8) = 82.73$, $p < 0.01$, a main effect of PTZ, $F(7, 08) = 22.66$, $p < 0.01$, a main effect of dose, $F(4, 98) = 9.16$, $p < 0.01$, and LOR × dose interaction, $F(4, 98) = 8.22$, $p < 0.01$. A significant LOR × PTZ interaction occurred. A post hoc Keul's test showed that doses of 0.5 and 0.10 mg/kg LOR administered singly differed significantly ($p < 0.05$) from PTZ. As with transitions, no significant difference was observed between the association of LOR chronic with acute PTZ and LOR singly administered.

Effects of Moclobemide Given Chronically, Singly, or in Association With Acute Pentylenetetrazole

Figure 2A shows the effect of MOC on the number of transitions. A three-way ANOVA showed a main effect of MOC, $F(7, 8) = 7.77$, $p < 0.01$, and a main effect of PTZ, $F(7, 8) = 27.22$, $p < 0.01$. A significant MOC × dose interaction and MOC × PTZ interaction occurred.

Comparison of the activity scores on time (Fig. 2B) indicated a main effect of MOC, $F(7, 08) = 100.17$, $p < 0.01$, a main effect of PTZ, $F(7, 08) = 14.83$, $p < 0.01$, a main effect of dose, $F(7, 08) = 13.07$, $p < 0.01$, and a significant MOC × dose interaction.

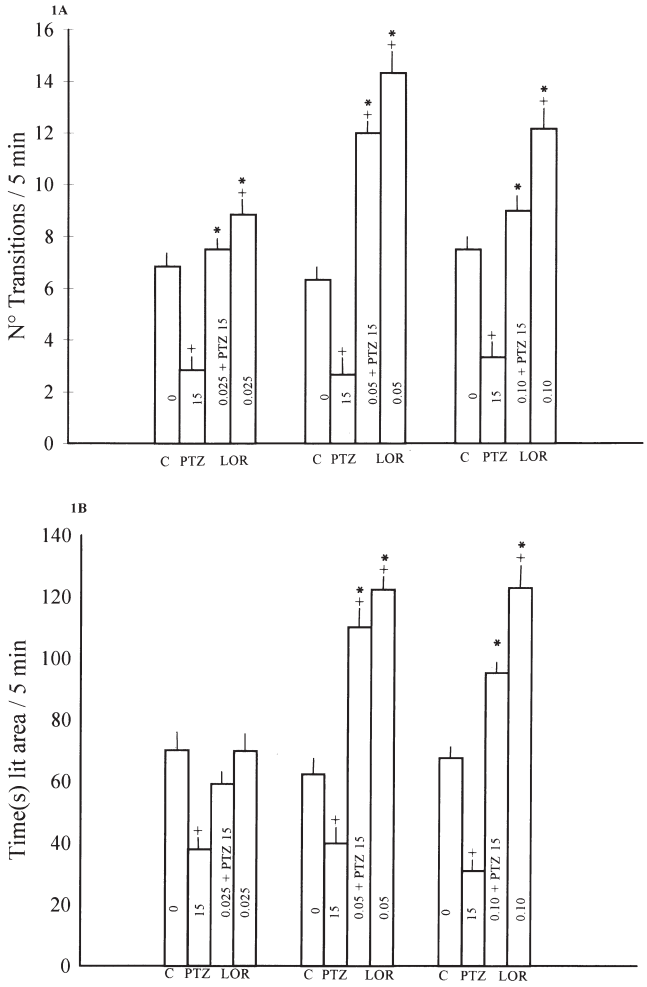

Fig. 1. Chronic effects of lorazepam (LOR) 0.025, 0.05, and 0.10 mg/kg IP in the light/dark aversion test in mice. All drugs, except pentylenetetrazole (PTZ), were administered once daily for 14 days. On day 15, an injection of the drug or vehicle was given 30 min before the light/dark aversion test. An anxiogenic-like behavior was induced by pretreatment with subconvulsant doses of PTZ (15 mg/kg IP) 45 min before testing. The number of transitions (A) and the time spent in the lit area (B) were scored over 5 min. Data are expressed as the mean ± SEM (n = 6 mice per group); †$p < 0.05$, post hoc Keul's test, significantly different from vehicle controls (0); *$p < 0.05$, post hoc Keul's test, significantly different from PTZ controls.

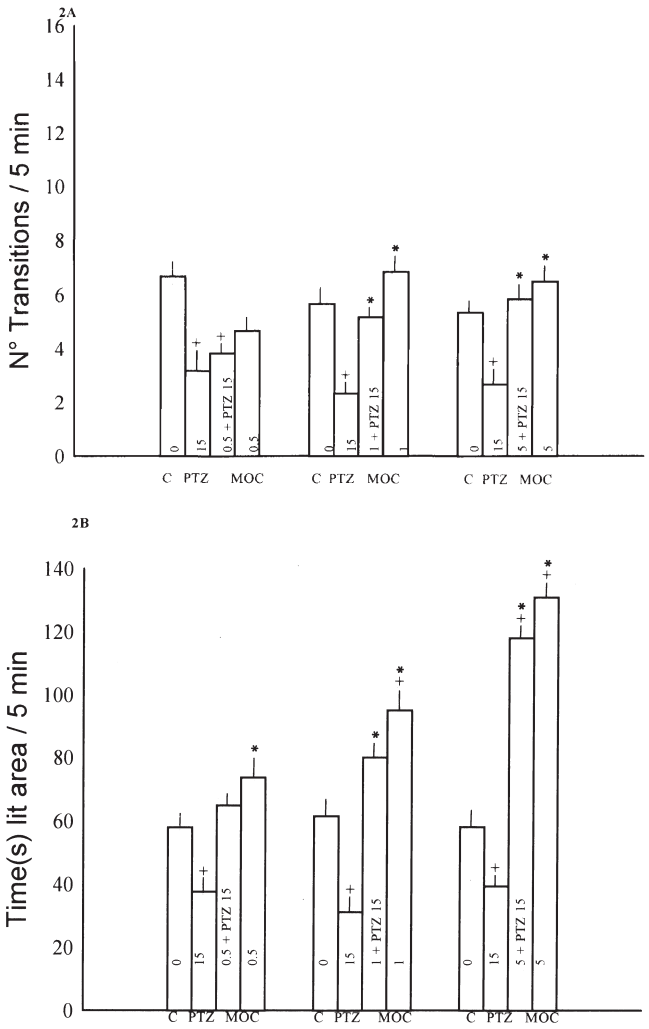

Fig. 2. Effects of moclobemide (MOC) 0.5, 1, and 5 mg/kg IP in the light/dark aversion test in mice. All drugs, except pentylenetetrazole (PTZ), were administered once daily for 14 days. On day 15, an injection of the drug or vehicle was given 30 min before the light/dark aversion test. An anxiogenic-like behavior was induced by pretreatment with subconvulsant doses of PTZ (15 mg/kg IP) 45 min before testing. The number of transitions (A) and the time spent in the lit area (B) were scored over 5 min. Data are expressed as the mean ± SEM (n = 6 mice per group); †$p < 0.05$, post hoc Keul's test, significantly different from vehicle controls (0); *$p < 0.05$, post hoc Keul's test, significantly different from PTZ controls.

A post hoc Keuls' test showed that doses of 0.5, 1, and 5 mg/kg MOC differed significantly ($p < 0.05$) from PTZ. There was no significant difference between the association of doses of 0.5, 1, and 5 mg/kg MOC with acute PTZ and MOC singly administered.

Effects of Selegiline Given Chronically, Singly, or in Association With Acute Pentylentetrazole

Figure 3A shows the effect of SEL on the number of transitions. A main effect of PTZ was seen, $F(7, 08) = 31.15$, $p < 0.01$. No significant interaction was seen as regards SEL × dose and SEL × PTZ. Further statistical analysis indicated that mice treated with doses of 20 mg/kg SEL differed significantly ($p < 0.05$) from groups treated with PTZ.

With respect to the time spent in the lit area (Fig. 3B), three-way ANOVA showed a main effect of PTZ, $F(7, 8) = 55.21$, $p < 0.01$. No significant SEL × PTZ interaction occurred. A post hoc Newman–Keul's test showed that doses of 5 and 20 mg/kg SEL differed significantly from PTZ. The association of doses of 20 mg/kg SEL with acute PTZ indicated a significant difference vs. SEL singly administered.

DISCUSSION

This study confirms and extends our previous data on the anxiolytic-like effects of MOC given acutely in the open field and light/dark aversion test. In particular, the present experiments provide evidence that, like the reference anxiolytic

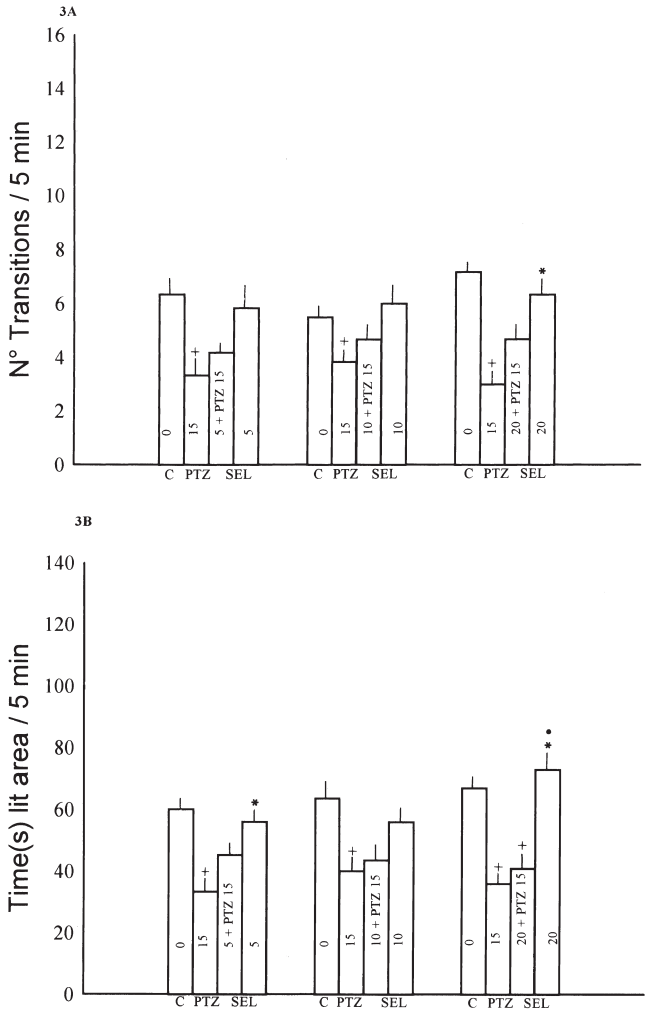

Fig. 3. Chronic effects of selegiline (SEL) 5, 10, and 20 mg/kg IP in the light/dark aversion test in mice. All drugs, except pentylenetetrazole (PTZ), were administered once daily for 14 days. On day 15, an injection of the drug or vehicle was given 30 min before the light/dark aversion test. An anxiogenic-like behavior was induced by pretreatment with subconvulsant doses of PTZ (I 5 mg/kg IP) 45 min before testing. The number of transitions (A) and the time spent in the lit area (B) were scored over 5 min. Data are expressed as the mean ± SEM ($n = 6$ mice per group); †$p < 0.05$, post hoc Keul's test, significantly different from vehicle controls (0); *$p < 0.05$, post hoc Keul's test, significantly different from PTZ controls; •$p < 0.05$, post hoc Keul's test, significantly different from SEL 20+PTZ 15.

LOR, 0.5, 1, and 5 mg/kg of MOC, given chronically, significantly reduced anxiogenic-like behavior in the "standard" version of the test (with light alone as the stimulus) and in the "enhanced" version (with pretreatment with the anxiogenic PTZ 15 mg/kg). More precisely, our mice showed reduced aversive behavior for the light area in the light/dark aversion test.

In fact, consistent with the present data, studies (30) have showed that, in mice, the best way of measuring the effect of anxiolytic agents is the time spent in the lit area, while a decrease in the time spent in the lit area as well as in the number of transitions are characteristic of an anxiogenic response (7,18). In the present study, this response was reduced after

TABLE 1

ACUTE EFFECTS OF MOCLOBEMIDE (MOC) 0.5, 1, AND 5 mg/kg ON THE BEHAVIOR OF MICE IN THE LIGHT/DARK AVERSION TEST

Treatment	Number of Transitions/5 min	Time(s) Lit Area/5 min
C‡	8.20 ± 0.72	78.01 ± 5.70
MOC		
0.5†	6.08 ± 0.98	82.39 ± 10.39
1‡	9.80 ± 0.93	139.91 ± 12.77*
5‡	8.87 ± 0.31	114.13 ± 10.12*

MOC or vehicle (C) were administered IP 30 min before testing. Data are expressed as the mean ± SEM.

*$p < 0.05$ significantly different from C.

†de Angelis (unpublished data).

‡From (9).

MOC and LOR chronically administered, suggesting an anxiolytic effect.

In particular, the following aspects of these findings deserve some comment. First, the anxiolytic-like effects of MOC were virtually the same after single (Table 1) and multiple (Fig. 2A and 2B) treatment, suggesting that no tolerance has developed as a result of the chronic treatment.

Other studies have proposed the anxiolytic-like properties of MOC. More precisely, in the mouse defense-test battery, chronic treatment with the same range doses of our experiments showed a behavioral profile consistent with an anxiolytic-like effect, although weaker than that of classical anxiolytic-drugs (12).

With respect to SEL, an irreversible inhibitor of MAO-B, our data show that chronic treatment with SEL at all doses given in association with PTZ, led to nonsignificant variations in activity in both measures to the anxiogenic PTZ or vehicle controls (with the exception of SEL 20 mg/kg in time spent in the lit area). Only doses of 5 and 20 mg/kg administered chronically singly were able to increase the time spent in the lit area of the light/dark aversion test, when compared to PTZ controls, but not when compared to vehicle controls. In summary, these data suggest a lack of anxiolytic-like effects for SEL.

In this connection, it is pertinent to compare the present results with those obtained by other authors (4). More precisely, in the rat, it was reported that, acute or chronic treatment with a MAO-A (chlorgyline) or MAO-B selective irreversible inhibitors (selegiline) failed to exert an anxiolytic effect (i.e., an anticonflict effect). Therefore, it is suggested that chronic inhibition of either isoenzyme alone is ineffective in reducing anxiety-like behavior, and that inhibition of both MAO-A and MAO-B is necessary to bring about the anxiolytic-like effects resulting from chronic IMAO treatment.

In other experiments using doses selective for MAO-B, SEL failed to bring about any change in activity in mice or rats, except when used in combination with phenylethylamine (3,27). On the contrary, other studies in the rat reported an increase in behavioral activity. It should be pointed out that this increase was evident only at high doses (10 mg/kg or higher) (3,17). Also, in a dog model, chronic oral studies (21) showed no significant effects on open-field scores, while acute oral studies showed a dose-dependent effect (increase in locomotion at 2 mg/kg or higher, but not increased exploratory behavior) (14).

Some comments should also be made about the metabolism of SEL and MOC. SEL is metabolized to L-amphetamine

and methamphetamine, and therefore, produces its effects on behavior mainly through its formation of these active metabolites (10,15).

Regarding MOC, it was found in a rat model that one of the metabolites of MOC (Ro 16-6491) exhibits selective MAO-B inhibitory activity (24), suggesting that the anxiolytic activity is due to the inhibition of MAO-B activity. But the fact that SEL, which is a selective inhibitor of MAO-B, has no significant anxiolytic profile, supports the hypothesis that the anxiolytic-like effects of MOC are a result of MAO-A inhibition, i.e., MOC itself.

Clearly, because the metabolism of MOC in rats is different in quantitative the following observations must be made. In humans, two of the other metabolites of MOC appear in plasma, namely Ro 12-5637 and Ro 12-8095. Most importantly, Ro 12-5637, present in trace concentrations, retains some MAO-A activity, while Ro 12-8095 is inactive (19). It may, therefore, be argued that the anxiolytic-like properties of MOC in humans may be correlated mainly to MOC itself and its metabolite that inhibits MAO-A enzyme.

In conclusion, these findings in the "standard" version of the light/dark aversion test with only light as the stimulus or the "enhanced" version with the pretreatment with the anxiogenic PTZ, provide additional evidence for the anxiolytic-like profile of MOC administered chronically in the mouse.

ACKNOWLEDGEMENTS

The authors would like to thank Chiesi Farmaceutici and Roche for supplying the samples of selegiline and moclobemide, respectively.

REFERENCES

1. Belzuing, C.; Misslin, R.; Vogel, E.; Dodd, R. H.; Chapounthier, G.: Anxiogenic effects of methyl-β-carboline-3-carboxylate in a light-dark choice situation. Pharmacol. Biochem. Behav. 28:29–33; 1987.
2. Berlin, I.; Saïd S.; Spreux-Varoquaux, O.; Launay, J.M.; Olivares, R.; Millet, V.; Lecrubier, Y.; Puech, A. I.: A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. Clin. Pharmacol. Ther. 58:444–452; 1995.
3. Braestrup, C.; Anderson, H.; Randrup, A.P.: The monoamine oxidase B inhibitor deprenyl potentiates phenylethylamine behavior in rats without inhibition of catecholamine metabolite formation. Eur. J. Pharmacol. 34:181–187; 1975.
4. Commissaris, R. L.; Humrich, J.; Johns, J.; Geere, D. G.; Fontana, D. J.: The effects of selective and non-selective monoamine oxidase (MAO) inhibitors on conflict behavior in the rat. Behav. Pharmacol. 6:195–202; 1995.
5. Da Prada, M.; Kettler, R.; Keller, H. H.; Burkard, W. P.; Muggli-Maniglio; Haefely, W.: Neurochemical profile of moclobemide, a short activating and reversible inhibitor of monoamine oxidase type A. J. Pharmacol. Exp. Ther. 248:400–414; 1989.
6. Da Prada, M.; Kettler, R.; Burkard, W. P.; Haefely, W.: Some basic aspects of reversible inhibitors of monoamine oxidase-A. Acta Psychiatr. Scand. 360S:7–12; 1990.
7. de Angelis, L.: The anxiogenic-like effects of pentylenetetrazole in mice treated chronically with carbamazepine or valproate. Methods Find. Exp. Clin. Pharmacol. 14:767–771; 1992.
8. de Angelis, L.: Comparative effects of valproate, anxiolytic, or anxiogenic drugs on the light/dark aversion test. Drug Dev. Res. 25:331–338; 1992.
9. de Angelis, L.: Experimental anxiety and antidepressant drugs: The effect of moclobemide, a selective reversible MAO-A inhibitor, fluoxetine and imipramine in mice. Naunyn Schmiedebergs Arch. Pharmacol. 354:379–383; 1996.
10. Engberg, G.; Elebring, T.; Nissbrandt, H.: Deprenyl (Selegiline) a selective MAO-B inhibitor with active metabolites; Effects on locomotor activity, dopaminergic neurotransmission and firing rate of nigral dopamine neurons. J. Pharmacol. Exp. Ther. 259:841–847; 1991.
11. Giorgiev, S.; Hranov, L.: Reversible MAO-A inhibitors in the treatment of panic disorder. Eur. Neuropsychopharmacol. 6 S1: P-43; 1996.
12. Griebel, G.; Perrault, D.J.; Sanger, D.J.: Evaluation of the anxiolytic and anti-panic potential of befloxatone and moclobemide in mice. Biol. Psychiatry 42:42S; 1997.
13. Haefely, W.; Burkard, W.P.; Cesura, A.M.; Kettler, R.; Lorez, H.P.; Martin, JR.; Richards, I.G.; Scherschlicht, R.; Da Prada, M.: Biochemistry and pharmacology of moclobemide, a prototype RIMA. Psychopharmacology (Berlin) 106:S6–S14; 1992.
14. Head, E.; Milgram, N.W.: Changes in spontaneous behavior in the dog following oral administration of l-deprenyl. Pharmacol. Biochem. Behav. 43:749–757; 1992.
15. Heinonen, E.H.; Myllylä, V.; Sotaniemi, K.; Lamintausta, R.; Salonen, J.S.; Anttila, M.; Savijarvi, M.; Kotila, M.; Rinne, U.K.: Pharmacokinetics and metabolism of selegiline. Acta Neurol. Scand. 80(Suppl 126):83–91; 1989.
16. Katschnig, H.; Berger, P.: MAOIs in social phobia. Eur. Neuropsychopharmacol. 5:S17–S22; 1995.
17. Knoll, J.; Ecseri, Z.; Magyar, K.; Satory, E.: Novel(−)-deprenyl-device selective inhibitors of B-type monoamine oxidase. The relation of structure to their action. Biochem. Pharmacol. 27: 1739–1747; 1978.
18. Lal, H.; Emmett-Oglesby, M.W.: Behavioural analogues of anxiety. Neuropharmacology 22:1423–1441; 1983.
19. Mayersohn, M.; Guentert, T.W.: Clinical pharmacokinetics of the monoamine oxidase-A inhibitor moclobemide. Clin. Pharmacokinet. 29:292–332; 1995.
20. Meienberg, O.; Amsler, F.: Moclobemide in the prophylactic treatment of migraine. A retrospective analysis of 44 cases. Eur. Neurol. 36:109–112; 1996.
21. Milgram, N.W.; Ivy, G.O.; Murphy, M.P.; Head, E.; Wu, P.H.; Ruehl, W.W.; Yu, P.H.; Durden, D.A.; Davis, B.A.; Boulton, A.A.: Effects of chronic oral administration of l-deprenyl in the dog. Pharmacol. Biochem. Behav. 51:421–428; 1995.
22. Miura, H.; Naoi, M.; Nakahara, D.; Ohta, T.; Nagatsu, T.: Effects of moclobemide on forced-swimming stress and brain monoamine levels in mice. Pharmacol. Biochem. Behav. 53:469–475; 1996.
23. Onaivi, E.S.; Martin, B.R.: Neuropharmacological and psychological validation of a computer-controlled two compartment black and white box for the assessment of anxiety. Prog. Neurophsychopharmacol. Biol. Psychiatry 13:963–976; 1989.
24. Schoerlin, M.P.; Da Prada, M.: Species-specific biotransformation of moclobemide: A comparative study in rats and humans. Acta Psychiatr. Scand. 360S:108–110; 1990.
25. Tiller, J.W.G.: Clinical overview on moclobemide. Prog. Neuropsychopharmacol. Biol. Psychiatry 17:703–712; 1993.
26. Trott, G.E.; Friese, H.J.; Menzel, M.; Nissen, G.: Use of moclobemide in children with attention deficit hyperactivity disorder. Psychopharmacology (Berlin) 106:S134–S136; 1992.
27. Turkish, S.; Yu, P. H.; Greenshaw, A.A.: Monoamine oxidase-B inhibition: A comparison of in vivo and ex vivo measures of reversible effects. J. Neural. Transm. 74:141–148; 1988.
28. Ward, C.: Does selegiline delay progression of Parkinson's disease? A critical re-evaluation of the DATAOP Study. J. Neurol. Neurosurg. Psychiatry 57:217–220; 1994.
29. Wesnes, K.; Anand, R.; Lorscheid, T.: Potential of moclobemide to improve cerebral insufficiency identified using a scopolamine model of aging and dementia. Acta Psychiatr. Scand. 360S:71–72; 1990.
30. Young, R.; Johnson, D.N.: A fully automated light/dark apparatus useful for comparing anxiolytic agents. Pharmacol. Biochem. Behav. 40:739–743; 1991.