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Anxiolytic and sedative effects of 5-HT$_{1A}$ ligands, 8-OH-DPAT and MDL 73005EF, in mice

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THE actions of the 5-HT$_{1A}$ receptor ligands, MDL 73005EF and 8-OH-DPAT, were assessed in mice. They were confronted with a free exploratory test especially adapted to reveal sedation, and with a two-box light/dark choice situation validated for the detection of anti-anxiety agents.[1] Both drugs were found to have sedative properties at high doses and anxiolytic-like effects at lower doses. The results show that both drugs have a comparable profile of action to that of benzodiazepines in the two-box light/dark procedure. These findings are in line with earlier reports describing anxiolytic effects of 5-HT$_{1A}$ receptor ligands in different animal models of anxiety.

Key words: MDL 73005EF, 8-OH-DPAT, Mice, Free exploratory test, Two-box light/dark procedure, Anxiolysis, Sedation

Introduction

There is now growing evidence for the involvement of 5-HT in the control of anxiety.[2,3,4,5] For example, several authors have found anxiolytic-like effects with 5-HT$_{1A}$-related compounds such as buspirone, gepirone, ipsapirone, 5-MeODMT, 8-OH-DPAT and MDL 73005EF in various animal models of anxiety.[6] Interestingly, in a number of drug discrimination studies, it has been demonstrated that these drugs all produce similar 5-HT$_{1A}$-related cues which differ from those induced by benzodiazepines.[7] These findings suggest that they likely produce their effects through a 5-HT$_{1A}$-mediated mechanism.[8] This view is further substantiated by the hypothesis that an agonist effect at somatodendritic 5-HT$_{1A}$ receptors which leads to a decrease in raphé cell firing is responsible for their anxiolytic effects,[9,10] emphasizing the distinction between terminal and cell body 5-HT autoreceptors.[11]

Costall *et al.*[12] found that in a light/dark choice procedure buspirone reduced the avoidance responses of mice to the brightly illuminated area. Thus, it was of interest to compare the putative antianxiety effects of 8-OH-DPAT with MDL 73005EF, recently described as a potent and highly selective ligand for 5-HT$_{1A}$ receptors.[9,13] In our first experiment (1) we examined the effects of these compounds in a free exploratory test which allows measurement of changes in novelty-seeking behaviour as well as in locomotor and rearing activities and hence detects any sedative drug action. In experiment 2 we investigated the effects of 8-OH-DPAT and MDL 73005EF in an animal test of anxiety, the light/dark choice procedure conceived by Crawley and Goodwin,[14] modified and behaviourally validated by Misslin *et al.*[1]

Materials and Methods

Male Swiss albino mice from Centre d'Elevage R. Janvier were used. They were ten weeks old at the time of testing, and were tested during the dark phase.

8-OH-DPAT (a gift from Hoffmann-La Roche Co., Basle) and MDL 73005EF (a gift from Merrell Dow Research Institute, Strasbourg) were dissolved in saline and administered i.p., 30 min before testing, at different concentrations in a volume of 10 ml kg^{-1} body wt.

Experiment 1: The apparatus consisted of a polyvinyl box (30 × 20 × 20 cm) subdivided into six equal, square units and covered with Plexiglas. It could be temporarily divided in half by means of three partitions. Each mouse was placed for approximately 24 h in one-half of the apparatus with the temporary partitions inserted. Approximately 24 h after this familiarization, each mouse was exposed to both the familiar and novel environments by the removal of the temporary partitions. The mouse was then observed in red light for 10 min. The time spent by mice in the novel compartment (novelty preference), the number of units entered (locomotion) as well as the number of rearing responses were recorded.

Experiment 2: The apparatus consisted of two polyvinyl chloride boxes (20 × 20 × 14 cm) covered with Plexiglas. One of these boxes was kept dark. A light from a 100 watt desk lamp above the other provided the only room illumination. An opaque plastic tunnel (5 × 7 × 10 cm) separated the dark box from the illuminated one. The subjects were individually tested in 5 min sessions in the apparatus described above. All mice were placed in the illuminated box to initiate the test session. The amount of time spent by mice in the illuminated box and the number of tunnel crossings (transitions) were recorded minute by minute, during 5 min after the first entry into the dark box.

Results

Experiment 1: Analysis of variance revealed significant differences among groups for novelty preference in

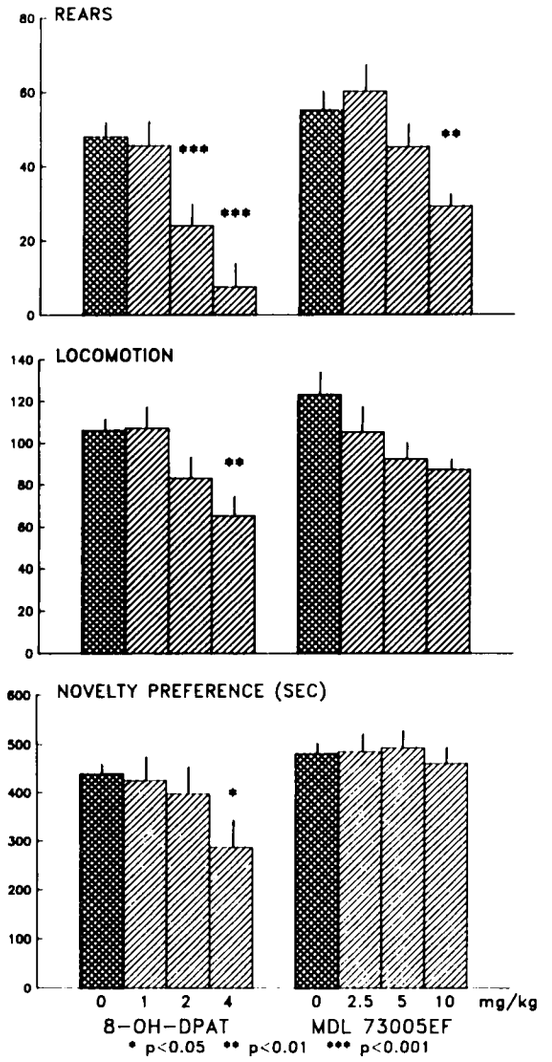

FIG. 1. Effects of 8-OH-DPAT and MDL 73005EF on the behaviour of mice confronted with a free exploratory test (8-OH-DPAT: $n = 15$; MDL 73005EF: $n = 10$; s.e.m. indicated above each bar).

mice treated with 8-OH-DPAT ($F(3,56) = 5.20$; $p < 0.003$), but not in mice treated with MDL 73005EF ($F(3,36) = 0.70$), for locomotion in mice treated with 8-OH-DPAT ($F(3,56) = 4.96$; $p < 0.004$), but not in mice treated with MDL 73005EF ($F(3,36) = 2.64$) and for the rearing behaviour in mice treated with 8-OH-DPAT ($F(3,56) = 27.29$; $p < 0.001$) as well as in mice treated with MDL 73005EF ($F(3,36) = 5.55$; $p < 0.003$). Figure 1 shows that 8-OH-DPAT significantly decreased novelty preference and locomotion at the highest dose (4 mg kg^{-1}) as well as the rearing behaviour at 2 and 4 mg kg^{-1}. MDL 73005EF significantly decreased the rearing behaviour only at the highest dose (10 mg kg^{-1}).

Experiment 2: In mice treated with 8-OH-DPAT, ANOVA revealed significant group differences for time in the lit box ($F(3,76) = 4.29$; $p < 0.007$) and for the number of transitions ($F(3,76) = 3.06$; $p < 0.03$).

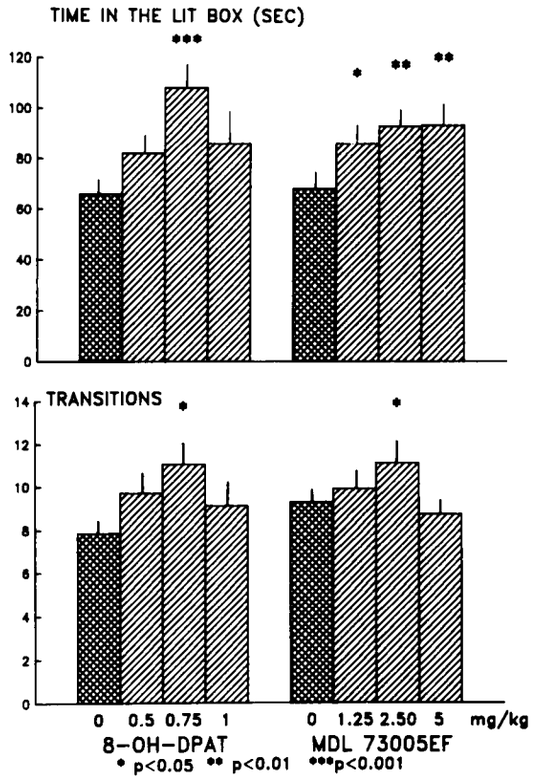

FIG. 2. Effects of 8-OH-DPAT and MDL 73005EF on the behaviour of mice in the light/dark choice procedure (8-OH-DPAT: $n = 20$; MDL 73005EF: saline: $n = 40$; drug: $n = 25$).

Figure 2 shows that this drug at 0.75 mg kg^{-1} significantly increased time in the lit box and the number of transitions. In mice treated with MDL 73005EF, ANOVA revealed significant group differences for time in the lit box ($F(3,11) = 6.62$; $p < 0.001$) and for the number of transitions ($F(3,11) = 3.50$; $p < 0.001$). Figure 2 shows that the drug significantly increased time in the lit box at all doses and the number of transitions at only 2.5 mg kg^{-1}.

Discussion

The present results provide evidence that 8-OH-DPAT and MDL 73005EF induced a decrease of all three behavioural parameters recorded in a free exploratory test, this effect appearing to be a behavioural sedation. However, it is to be noted that statistical analysis indicates that the sedative effects of 8-OH-DPAT become significant for all parameters, at least at the highest dose, whereas MDL 73005EF significantly decreased only the rearing behaviour at the highest dose, although the dose range of the latter drug was wider. Consequently, these data suggest that 8-OH-DPAT has more potent sedative properties than MDL 73005EF. In general, these results are in line with earlier reports of locomotor impairment after 8-OH-DPAT or MDL 73005EF in rat.[9,15] Never-

theless, Dourish *et al.*[16] found that 8-OH-DPAT (0.250–4 mg kg^{-1}) caused a dose-dependent locomotor stimulation and serotonin-related stereotyped behaviour.

Crawley and Goodwin[14] found that benzodiazepines increase the number of transitions between a brightly-lit environment and a dark one, while Belzung *et al.*,[17] using a two-box test system,[1] found that these drugs increase the time spent by mice in the lit box as well as their number of transitions. In the present study, the peripheral administration of 8-OH-DPAT and MDL 73005EF was found to have a comparable profile of action to that of benzodiazepines. It can be observed that the so-called anxiolytic-like effects appear at doses which were devoid of sedative effects in the free exploratory test. These results are in agreement with other reports of anxiolytic-like effects of these compounds in rat in different conflict procedures.[9,15] In addition, our findings also closely resemble those obtained by Costall *et al.*[12] with peripheral or dorsal raphé nucleus injection of buspirone, in mice confronted with a two-compartment box divided into a dark area and a brightly-lit one. Interestingly, it has been demonstrated that anxiolytic-like effects of 8-OH-DPAT are clearest in animals subjected to stress, a high state of arousal interacting with the anti-anxiety effects of this drug.[18] Previously, it has been shown that in stressful situations where animals are forced into novel, brightly illuminated enclosures, as in the two-box light/dark test, they exhibit specifically anxious emotional responses.[19,20] However, although the present findings support the conclusion that 8-OH-DPAT and MDL 73005EF have an anxiolytic action, it must be emphasized that other authors have failed to find such effects with 8-OH-DPAT or to even observe anxiogenic-like actions.[6] The diversity of procedures, animal species or strains, and doses may partly explain the discrepancy of results. In fact, Broekkamp and Jenck[21] have recently pointed out that no single animal model is universally useful for identifying all potential anxiolytic drugs.

Conclusion

The present findings confirm earlier reports describing anxiolytic-like effects of 5-HT$_{1A}$ receptor ligands and furthermore suggest that MDL 73005EF is less sedative than 8-OH-DPAT.

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