ELSEVIER

Pharmacology Biochemistry and Behavior, Vol. 54, No. 1, pp. 123–128, 1996

0091-3057/96 $15.00 + .00

SSDI 0091-3057(95)02108-6

Anxiolytic Effects in the Plus-Maze of 5-HT_{1A}-Receptor Ligands in Dorsal Raphé and Ventral Hippocampus

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FILE, S. E. AND L. E. GONZALEZ. *Anxiolytic effects in the plus-maze of 5-HT_{1A}-receptor ligands in the dorsal raphé and ventral hippocampus.* PHARMACOL BIOCHEM BEHAV **54**(1) 123–128, 1996.—The response of rats naive to, or experienced with, the elevated plus-maze test of anxiety was observed following direct administration of the 5-HT_{1A}-receptor agonist (±)-8-hydroxy-dipropylaminotetralin (8-OH-DPAT) (50, 100, or 200 ng) or antagonist tertatolol (3 μg) into the dorsal raphé nucleus or bilaterally into the ventral hippocampus. In rats naive to the plus-maze, neither drug had a significant effect when microinjected into the dorsal raphé nucleus. However, in rats experienced with the plus-maze, 8-OH-DPAT (100 and 200 ng) had significant anxiolytic effects when administered to the dorsal raphé nucleus, which were antagonised by tertatolol (3 μg); this suggests they were mediated by 5-HT_{1A} receptors. Hyperactivity (increased number of closed-arm entries) was found following bilateral injection of 8-OH-DPAT (100 ng) into the ventral hippocampus of rats naive to the plus-maze. This was not completely antagonised by tertatolol (3 μg). Interestingly, tertatolol (3 μg) itself had an anxiolytic effect which was not antagonised by 8-OH-DPAT (100 ng), suggesting the effect was not mediated by 5-HT_{1A} receptors, and indeed other actions of tertatolol, such as those on 5-HT_{1B} or β-adrenergic receptors could have been involved. In rats experienced with the plus-maze, tertatolol (3 μg) again had a significant anxiolytic effect when administered bilaterally to the ventral hippocampus, and again, this was not antagonised by 8-OH-DPAT (100 ng). These results demonstrate that both the intracerebral location of the injection and test experience profoundly influence the effects of 5-HT_{1A} ligands on behaviour of rats in the elevated plus-maze test of anxiety.

Dorsal raphé Ventral hippocampus Anxiety Hyperactivity 5-HT_{1A} receptors β-Receptors Plus-maze

THE POSSIBLE importance of 5-HT_{1A} receptors in anxiety was raised by evidence that the clinically effective anxiolytic buspirone was a 5-HT_{1A}-receptor agonist/partial agonist (17, 27). 5-HT_{1A} receptors are found on the cell bodies of the raphé nuclei, where they act as autoreceptors controlling neuronal firing rate, and also postsynaptically in the raphé projection areas. It has been suggested (4) that the anxiolytic effects of 5-HT_{1A}-receptor agonists arise through stimulation of 5-HT_{1A} autoreceptors, leading to reduced 5-HT neuronal firing rate (26) and a decrease of 5-HT release in limbic regions such as the ventral hippocampus (14,25). In support of this hypothesis, administration of the 5-HT_{1A}-receptor agonist (±)-8-hydroxy-dipropylaminotetralin (8-OH-DPAT) directly into the dorsal raphé nucleus has been shown to produce anxiolytic effects in the social interaction test (12,13,20) and in foot-shock-induced ultrasonic vocalisations (24). The anxiolytic effect in the social interaction test of 8-OH-DPAT administration to the DRN appeared to be mediated by an agonist action at 5-HT_{1A} receptors, because it was antagonised by the 5-HT_{1A}-receptor antagonist tertatolol (13).

In contrast to the clear anxiolytic effects found in the social interaction test after administration of 8-OH-DPAT to the dorsal raphé nucleus, none were found after administration to the ventral hippocampus (13). However, in the low-light test condition, 8-OH-DPAT increased locomotor activity; this effect was antagonised by tertatolol.

The purpose of the present study was to examine the effects in the elevated plus-maze test of anxiety of the 5-HT_{1A}-receptor agonist 8-OH-DPAT and the 5-HT_{1A} receptor antagonist tertatolol (16,21) after administration to the dorsal raphé

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nucleus, or bilaterally to the ventral hippocampus. These two drugs were selected because they are soluble in artificial cerebrospinal fluid (CSF) at neutral pH, and hence are ideal candidates for central administration. The doses of the drugs tested were based on the range found to be effective in these brain regions when assessed in the social interaction test of anxiety (13). The interest in extending our studies to the plus-maze comes from the accumulating evidence that different animal tests are measuring different aspects of anxiety. Factor analysis has shown that the social interaction test and elevated plus-maze are measuring different underlying factors, and hence, each may be pertinent to different anxiety disorders or to different aspects of anxiety (6). Furthermore, there is evidence that the social interaction and elevated plus-maze tests are differentially sensitive to systemically administered 5-HT_{1A}-receptor agonists. The social interaction test has consistently detected anxiolytic actions or no effect, whereas the plus-maze has in general revealed anxiogenic actions (10). There is also evidence that previous experience of the plus-maze will modify an animal's response to anxiolytics (5,28), and factor analysis showed that the scores from naive and plus-maze-experienced rats reflected independent underlying factors (7,9). We therefore examined the effects of 8-OH-DPAT and tertatolol in rats both naive to, and experienced with, the plus-maze.

METHOD

Animals

Male, hooded Lister rats, weighing 200–300 g (Olac, Bicester, UK), were singly housed following surgery and allowed 7 days recovery before testing. Because of the importance of the history of handling to behaviour in the plus-maze, all of our rats were extensively handled for at least 1 week before surgery. To keep the cannulae patent, each day they were gently wrapped in a cloth and the stylets were replaced. Food and water were freely available, and the room in which they were housed was lit with dim light and maintained at 22°C. Lights were on from 0700 to 1900 h.

Apparatus

The plus-maze was made of wood and consisted of two opposite open arms 50 × 10 cm, and two opposite arms enclosed by 40-cm-high walls. The arms were connected by a central 10 × 10 cm square, and thus the maze formed a plus shape. The maze was elevated 50 cm from the floor and lit by dim light. A closed-circuit television camera was mounted vertically over the maze, and the behaviour was scored from a monitor in an adjacent room. All scores were entered directly into an IBM computer. Changes in the percentage of time spent on the open arms indicate changes in anxiety (19), whereas the number of closed-arm entries is the best measure of general activity in the maze (6).

Drugs and Chemicals

8-OH-DPAT hydrobromide (Research Biochemicals Incorporated, St. Albans, UK) and tertatolol hydrochloride (IRIS, Courbevoie, France) were dissolved in artificial CSF of the following composition (mM); NaCl 126.6, $NaHCO_3$ 27.4, KCl 2.4, KH_2PO_4 0.5, $CaCl_2$ 0.89, $MgCl_2$ 0.8, Na_2HPO_4 0.48, and glucose 7.1, pH 7.4. All drug concentrations reflect base weight.

Procedure

Surgery. Stereotaxic coordinates were verified histologically before each set of cannulations. Rats were anaesthetised by inhalation of 3% halothane (May and Baker, Dagenham, UK) in oxygen and positioned in a stereotaxic frame (Kopf Instruments, Tujunga, CA, USA). The skull was exposed and the incisor bar adjusted such that bregma and lambda were at the same height. For cannulation of the dorsal raphé nucleus, a 12-mm-long steel guide cannula (23 ga; Cooper's Needle Works Ltd., Birmingham, UK) was positioned at 7.4 mm posterior to bregma, lateral + 2.4 mm, and vertical −4.9 mm at an angle of 19°, siting it 2 mm above the dorsal raphé nucleus. For bilateral cannulation of the ventral hippocampus, 12-mm guide cannulae were positioned 4.8 mm posterior to Bregma, lateral ± 4.9 mm and vertical −5.9 mm. Cannulae were kept patent using 12-mm-long stainless-steel stylets (30 ga; Cooper's Needle Works).

Behavioural testing. On the test day, the rats were gently wrapped in a cloth and injected using needles constructed from 30-ga steel tubing which extended 2 mm below the tip of the indwelling cannula(e). Injections were 0.5 μl, except for 200 ng 8-OH-DPAT (0.6 μl), and were made over a period of 30 s; the needles were left in position a further 30 s to allow drug absorption. Three minutes later, the rat was placed in the

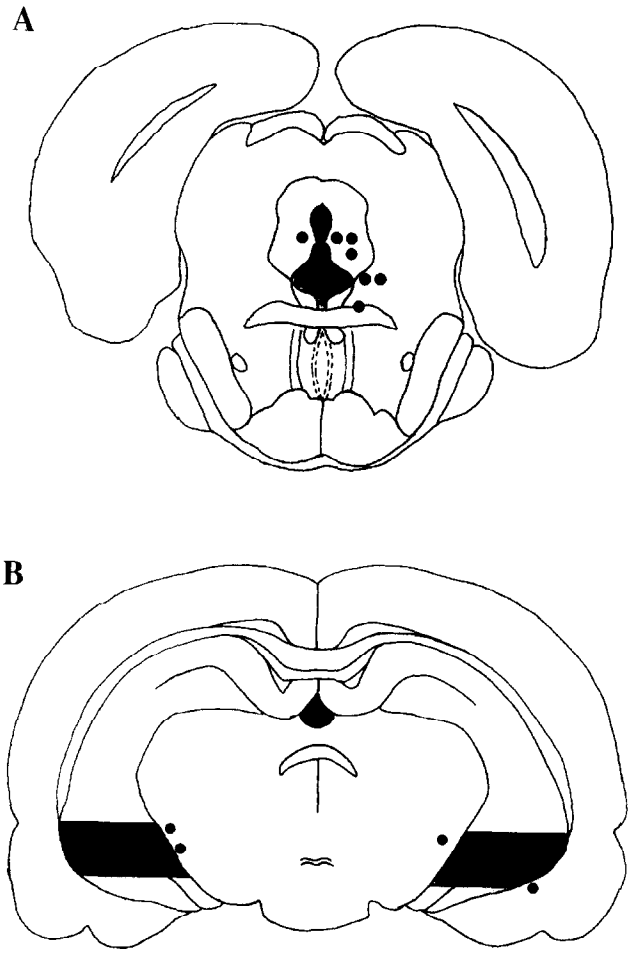

FIG. 1. Coronal sections through the rat brain showing the target areas (shaded) of the dorsal raphe nucleus (A) and ventral hippocampus (B). Examples of placements falling outside the target areas are shown by filled circles marking the sites of the tip of the injection needle.

TABLE 1

MEAN (±SEM) OF PERCENT TIME (s) IN THE OPEN ARM, PERCENT NO ENTRIES TO OPEN ARMS, TIME (s) IN THE CENTRE, AND NUMBER OF CLOSED-ARM ENTRIES MADE BY RATS IN TRIAL 1 IN THE PLUS-MAZE AFTER DORSAL RAPHÉ INJECTIONS

Dorsal Raphe (Trial 1)	*n*	% Time Open Arms	% No Entries to Open Arms	Time in Centre (s)	No Closed-Arm Entries
Vehicle	12	16.6 ± 1.9	30.0 ± 3.1	66.6 ± 6.1	10.5 ± 1.2
8-OH-DPAT					
50 ng	15	11.2 ± 2.8	22.6 ± 4.0	66.2 ± 3.6	7.9 ± 0.6
100 ng	19	15.6 ± 2.2	28.2 ± 2.5	60.2 ± 4.3	8.9 ± 0.8
200 ng	12	13.1 ± 2.4	25.2 ± 4.4	63.5 ± 3.5	9.3 ± 0.8
Tertatolol 3 μg	8	13.3 ± 1.7	30.4 ± 2.0	66.5 ± 6.5	9.6 ± 0.8

central square of the plus-maze and its behaviour observed for 5 min by an observer blind to the drug treatment. The numbers of entries onto open and closed arms and the times spent in open and closed arms and in the central square were scored. The animals were tested between 0800 and 1300 h in an order randomised for drug treatment, and the maze thoroughly wiped after each trial. Testing took place over 2 days, and vehicle control animals were tested on each day. In separate experiments, rats naive to the plus-maze (Trial 1) or experienced with it (Trial 2) were tested. Those tested after central injections on their second trial in the plus-maze had received a previous 5-min undrugged exposure to the maze 4 days earlier. A minimum of eight rats was allocated to each group; where $n < 8$, this is due to exclusions after the verification of cannula placements. Larger group sizes arose when the testing of a group was spread over more than 1 day. Vehicle controls were included on every test day.

Dorsal raphé nucleus. Rats were randomly allocated to the following groups: Trial 1: vehicle ($n = 12$); 8-OH-DPAT 50 ng ($n = 15$), 100 ng ($n = 19$), or 200 ng ($n = 12$); tertatolol 3 μg ($n = 8$). Trial 2: vehicle ($n = 11$), 8-OH-DPAT 50 ng ($n = 7$), 100 ng ($n = 7$), 200 ng ($n = 12$); tertatolol 3 μg ($n = 5$); tertatolol 3 μg plus 8-OH-DPAT 200 ($n = 7$).

Ventral hippocampus. Rats were randomly allocated to the following groups: Trial 1: those tested on the 1st test day, vehicle ($n = 11$); 8-OH-DPAT 50 ng ($n = 12$), 100 ng ($n = 11$); for the antagonism testing on the 2nd day, vehicle ($n = 11$); 8-OH-DPAT 100 ng ($n = 8$); tertatolol 3 μg ($n = 11$); tertatolol 3 μg plus 8-OD-DPAT 100 ng ($n = 8$). Trial 2: vehicle ($n = 21$); 8-OH-DPAT 100 ng ($n = 9$); tertatolol 3 μg ($n = 11$); tertatolol 3 μg plus 8-OH-DPAT 100 ng ($n = 10$).

Histology

At the end of behavioural testing, all animals were sacrificed, the brains removed, and the injection site verified histologically (18) by a person blind to drug treatment. Figure 1 depicts coronal slices through the dorsal raphé nuclei (7.4 mm posterior of bregma) and ventral hippocampus (4.8 mm posterior of bregma), and shows the target sites as shaded. Examples of placements for animals excluded from statistical analyses are shown as filled circles.

Statistics

The plus-maze scores were subjected to analysis of variance (ANOVA) with Duncan's post-hoc tests for differences between individual groups, the significance of which is shown in the figures. (Because of unequal group sizes, all significant differences were also verified with Mann-Whitney *U*-tests.) Antagonism of drug effects was assessed with a two-way ANOVA with 8-OH-DPAT and tertatolol as the two factors; a significant interaction between 8-OH-DPAT and tertatolol indicated antagonism.

RESULTS

Injections Into the Dorsal Raphé Nucleus

Trial 1. None of the drug doses tested had a significant effect on any of the measures recorded (Table 1).

Trial 2. 8-OH-DPAT had a significant dose-related anxiolytic effect [$F(3, 34) = 4.4$, $p < 0.01$], shown by increases in the percentage of time spent on the open arms (Fig. 2). The

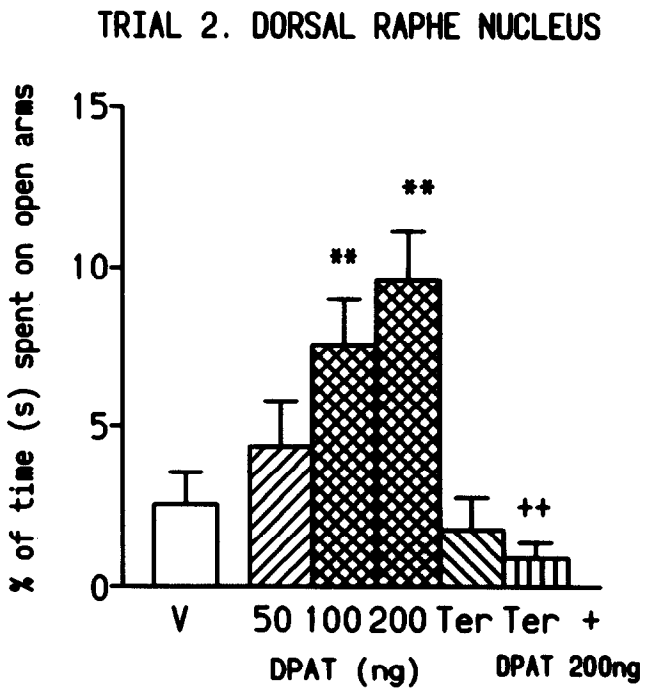

FIG. 2. Mean (±SEM) percent time (s) spent on the open arms in Trial 2 in the plus-maze by rats injected into the dorsal raphe nucleus with aCSF (V), 8-OH-DPAT (50, 100, 200 ng), tertatolol (3 μg), or tertatolol (3 μg) plus 8-OH-DPAT (200 ng). $^{**}p < 0.01$, compared with vehicle control; $^{++}p < 0.01$ compared with 8-OH-DPAT (200 ng).

anxiolytic effect of 200 ng was antagonised by tertatolol (8-OH-DPAT × tertatolol interaction [$F(1, 31) = 12.6$, $p < 0.001$], which alone was without significant effect (Fig. 2). None of the drugs had an effect on the number of closed arm entries (Table 2).

Four animals injected with 8-OH-DPAT had placements that fell outside the DRN. Their mean (±SEM) percent time on the open arm was 0.6 ± 0.6. This illustrates the anatomic specificity of the anxiolytic effect of DRN injections.

Injections Into the Ventral Hippocampus

Trial 1. The only significant effect of 8-OH-DPAT was an increased number of closed-arm entries [$F(2, 33) = 4.2$, $p < 0.05$], and this effect was significant for both 50- and 100-ng doses ($p < 0.05$). The higher dose of 8-OH-DPAT was chosen for the antagonism study. Once again, 8-OH-DPAT significantly increased the number of closed-arm entries [$F(1, 34) = 7.8$, $p < 0.01$], but this was not significantly antagonised by tertatolol (3 μg) (Fig. 3A). Tertatolol increased the percentage of time spent on the open arms [$F(1, 34) = 4.0$, $p < 0.05$]. This anxiolytic effect of tertatolol was not significantly antagonised by 8-OH-DPAT 100 ng [$F(1, 34) = 1.3$ $p > 0.10$] (Fig. 3B).

Trial 2. Tertatolol again had a significant anxiolytic effect, as shown by an increase in the percentage of time spent on the open arms [$F(1, 47) = 4.3$, $p < 0.05$], and this was not antagonised by 8-OH-DPAT (100 ng), which itself was without a significant effect (Fig. 3C). There were no changes in the number of closed-arm entries (Table 2).

DISCUSSION

The results of the present study demonstrate that rats naive to the plus-maze are less sensitive to the anxiolytic effects of 8-OH-DPAT administered to the dorsal raphé nucleus than those with previous plus-maze experience or those tested in the social interaction test. Although we cannot exclude the possibility that higher doses would have been anxiolytic in plus-maze naive rats, there was no trend in this direction. The difference in sensitivity to the anxiolytic effects of 8-OH-DPAT cannot be attributed to the effects of handling, because all of the rats in both the present study and in our previous social interaction experiment were extremely well handled. In agreement with results from the social interaction study (13), the anxiolytic effects of 8-OH-DPAT in plus-maze experienced rats seemed to be mediated by 5-HT_{1A} receptors, because they were antagonised by tertatolol. As was previously found in the social interaction test, the anxiolytic effects are specific, because they were not accompanied by a change in locomotor activity.

The insensitivity of rats naive to the plus-maze to the anxiolytic effects of dorsal raphé administration of 8-OH-DPAT could explain the relative difficulty in obtaining clear anxiolytic effects in this test with systemically administered 5-HT_{1A}-receptor agonists or partial agonists (11,23). Although the re-

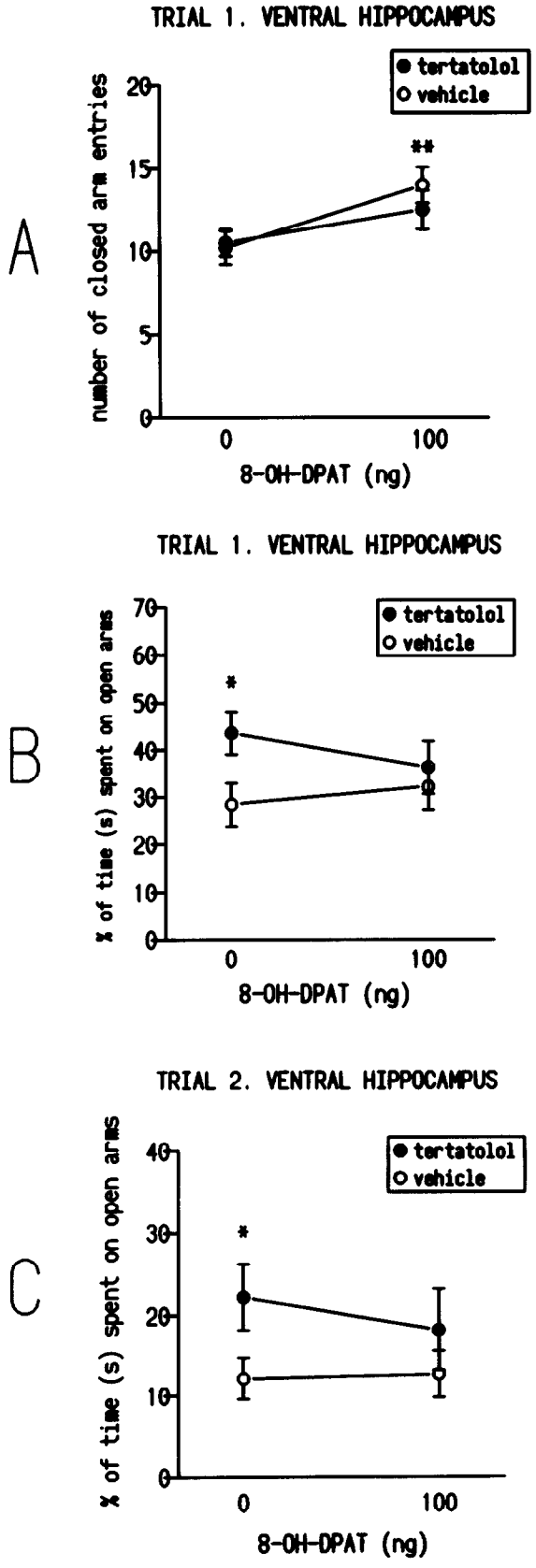

FIG. 3. Mean (±SEM) number of closed-arm entries (A) and percent time in open arms by rats tested in Trial 1 in the plus-maze (B) and percent time in open arms in Trial 2 (C) after bilateral injections to the ventral hippocampus. **$p < 0.01$, 8-OH-DPAT effect compared with vehicle control (A); *$p < 0.05$, tertatolol effect compared with vehicle control (B and C).

TABLE 2

MEAN (±SEM) OF NUMBER OF CLOSED ARM ENTRIES MADE IN TRIAL 2 IN THE PLUS-MAZE BY RATS AFTER DORSAL RAPHE OR VENTRAL HIPPOCAMPUS INJECTIONS

Trial 2	*n*	Closed-Arm Entries
Dorsal raphe		
Vehicle	11	11.8 ± 0.8
8-OH-DPAT		
50 ng	7	12.3 ± 1.2
100 ng	7	12.9 ± 1.2
200 ng	12	11.3 ± 0.6
Tertatolol		
3 g	5	12.0 ± 1.6
Tertatolol (3 μg) + DPAT (200 ng)	7	15.0 ± 1.8
Ventral hippocampus		
Vehicle	21	15.8 ± 1.3
8-OH-DPAT		
100 ng	9	16.8 ± 2.0
Tertatolol		
3 μg	11	16.5 ± 0.8
Tertatolol (3 μg) + DPAT (100 ng)	10	14.9 ± 1.4

sults from the present study might imply that plus-maze-experienced rats would be more sensitive to the anxiolytic effects of 5-HT_{1A}-receptor agonists, this does not seem to be the case. File (8) found that plus-maze-experienced rats were, if anything, more sensitive to the anxiogenic effects of low subcutaneous doses of buspirone. Two other tests of anxiety, the black-white crossing test and conditioned suppression of drinking, have also proved insensitive to dorsal raphé administration of 8-OH-DPAT and buspirone (2,3). It therefore seems that one way of differentiating among animal tests is in their sensitivity to modulation of dorsal raphé nucleus activity. In contrast to their lack of effects in the black-white crossing test and plus-maze Trial 1 after administration to the DRN, 8-OH-DPAT and buspirone had anxiolytic effects in both test situations after administration to the MRN [(2,3) and File et al., in preparation]. This anatomical dissociation lends further support to the existing evidence (7,9) that Trials 1 and 2 in the plus-maze are generating a different type of fear or anxiety. If this is the case, then the anxiolytic effect detected in Trial 2 after DRN application of 8-OH-DPAT cannot be simply attributed to a decreased baseline response of the control animals. In our studies on MRN application, there were also lower scores on Trial 2 in the control animals, but the effects of 8-OH-DPAT were not significant in Trial 2.

The effects of 8-OH-DPAT when administered to the ventral hippocampus also support those previously found in the social interaction test. The number of closed-arm entries is the best measure of locomotor activity in the plus-maze (6), and thus the increase in this measure found in the plus-maze-naive rats after 8-OH-DPAT administration to the ventral hippocampus would confirm the hyperactivity found in the low-light unfamiliar test condition of the social interaction test (13). The increase in closed-arm entries caused by 100 ng of 8-OH-DPAT was incompletely antagonised by 3 μg tertatolol (the combination of treatments no longer differed from controls, but also failed to differ from 8-OH-DPAT alone), suggesting that this dose was insufficiently high for complete antagonism in this brain region. In the social interaction test, complete antagonism of the hyperactivity induced by 50 ng 8-OH-DPAT was found with 3 μg tertatolol. No hyperactivity was found in the rats experienced with the plus-maze. The effects on locomotor activity of ventral hippocampal administration of 8-OH-DPAT have previously been found to depend on the light level; under high-light test conditions, 8-OH-DPAT decreased locomotor activity in the social interaction test (13). Thus, the details of the test conditions—in the present case, familiarity with the plus-maze—can modify the rat's sensitivity to the effects on locomotor activity of centrally administered 8-OH-DPAT.

The anxiolytic effects of tertatolol administration to the ventral hippocampus were not antagonised by 8-OH-DPAT, nor did the agonist administration have any effect on the measures of anxiety. Because 8-OH-DPAT did not have an anxiogenic effect, this suggests that the anxiolytic effects of tertatolol are probably not mediated by an antagonist action at 5-HT_{1A} receptors. Other possibilities are on 5-HT_{1B} receptors or β-adrenergic antagonistic actions (1). More extensive studies with the isomers of tertatolol and with other 5-HT_{1A}-receptor antagonists are needed to resolve the question of whether 5-HT_{1A}-receptor antagonism in the ventral hippocampus has anxiolytic effects. However, tertatolol administration to the ventral hippocampus did not have an anxiolytic effect in the social interaction test (13). The contrasting effects of tertatolol in the two tests once again raises the possibility of β-adrenergic modulation of behaviour in the plus-maze; it has previously been reported that the β-adrenergic agonist isoproterenol had an anxiogenic action in the elevated plus-maze, but not in the social interaction test (15). Further experiments are needed to explore the possible role of ventral hippocampal β-receptors in the modulation of anxiety. The results of Wright et al. (28), showing that the anxiolytic effects of 5-HT_{1A}-receptor agonists and partial agonists were not necessarily related to the reduction of 5-HT release in the ventral hippocampus, also support the lack of 5-HT_{1A}-receptor-mediated anxiolytic effects in this brain region. However, the report that systemic administration of the more selective 5-HT_{1A}-receptor antagonist (s)-WAY100135 has anxiolytic actions in the plus-maze (22) suggests that postsynaptic 5-HT_{1A} receptors in other brain regions are of importance.

ACKNOWLEDGEMENTS

L.E.G. is supported by a grant from Consejo Nacional de Investigaciones Científicas y Tecnológicas, Venezuela. The authors thank P. S. Mabbutt for expert technical assistance.

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