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Is the anxiolytic-like effect of acute 8-0H-DPAT mediated by 5-HT_{1A} receptors?

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ABSTRACT. In the study of the role of 5-HT_{1A} receptors in anxiety, dose-effect curve for the full 5-HT_{1A} receptor agonist 8-OH-DPAT was determined in rats exploring the elevated plus-maze. Dose of 0.5mg/kg, IP, of 8-OH-DPAT significantly increased the percentage of open arm entries and of time spent on the open arms, displaying an anxiolytic effect. Total number of entries into the enclosed arms, an index of locomotion, was also significantly increased. A lower (0.25mg/kg) and a higher dose (1.0mg/kg) of 8-OH-DPAT were ineffective. Contrastly, 2.0mg/kg, IP, of diazepam had a similar anxiolytic effect, but did not affect locomotion. The pretreatment with 1.0mg/kg of WAY 100135 did not antagonize the effects of 0.5mg/kg of 8-OH-DPAT on the indexes of anxiety and locomotion. These results show that 8-OH-DPAT has anxiolytic-like and locomotor stimulant effects in the elevated plus-maze. However, these effects do not seem to be mediated by $5HT_{1A}$ receptors.

Key words: anxiety, 8-OH-DPAT, elevated plus-maze, 5-HT_{1A} receptor, locomotion.

RESUMO. O efeito ansiolítico do 8-OH-DPAT é mediado por receptores 5-HT_{1A}? Para estudar o papel dos receptores 5-HT_{1A} na ansiedade, realizamos uma curva dose-efeito com o agonista pleno de receptores $5HT_{1A}$ administrado em ratos expostos ao labirinto em cruz elevado. A dose de 0,5mg/kg (IP) de 8-OH-DPAT aumentou significativamente a porcentagem de entradas e de tempo dispendido nos braços abertos. Esses resultados são indicativos de efeito ansiolítico. O número total de entradas nos braços fechados, que é um índice de atividade locomotora, também foi significativamente aumentado. Nenhuma alteração significativa foi verificada com a administração (IP) da dose mais baixa (0,25mg/kg) ou da dose mais alta (1,0mg/kg) do 8-OH-DPAT. Contrastantemente, a administração de 2,0mg/kg (IP) de diazepam produziu um efeito ansiolítico similar, mas não afetou a locomoção. O pré-tratamento com 1,0mg/kg do WAY 100135 não antagonizou os efeitos obtidos com a administração de 0,5mg/kg do 8-OH-DPAT sobre os índices de ansiedade e locomoção. Esses resultados demonstram que o 8-OH-DPAT produziu um efeito ansiolítico e estimulante de atividade locomotora no labirinto em cruz elevado. Entretanto, estes efeitos não parecem ser mediados por receptores 5-HT_{1A}.

Palavras-chave: ansiedade, atividade locomotora, labirinto em cruz elevado, 8-OH-DPAT, receptor 5-HT_{1A}.

SEROTONIN (5-HT) has been implicated in anxiety disorders and in the mode of action of anxiolytic and anxiogenic drugs (Graeff *et al.,* 1996). Among the subtypes of 5-HT receptors so far described, the 5-HT_{1A} receptor is particularly important with regard to anxiety, because the clinically useful anxiolytic and antidepressant buspirone is a partial 5-HT_{1A} receptor agonist (Goa and Ward, 1986; Taylor *et al.,* 1985). Other 5-HT_{1A} receptor agonists (1A agonists) such as gepirone, ipsapirone and flesinoxan have shown similar pharmacological properties in clinical studies (Ansseau *et al., 1*993; Bradford, 1993). Nonetheless, animal models of anxiety do not always detect the anxiolytic-like effect of 1A agonists. Although single administration of 1A agonists has marked anxiolytic effects in pigeons (Barrett *et al.,* 1986, 1989; Mansbach *et al., 1*988), results have been inconsistent in rats (Sanger, 1990). In the widely used elevated X or plus-maze model (Handley and McBlane, 1993; Pellow *et al.,* 1985), anxiolytic, anxiogenic and no effect have been reported (Griebel, 1995). An anxiogenic effect of the full 1A agonist 8-OH-DPAT changes to anxiolytic when the

illumination of the elevated plus-maze is altered (McBlane *et al.,* 1992; Griebel *et al.,* 1993). Another problem exists: clinical effects of 1A agonists appear only after two weeks of continuous administration. The first dose may even enhance anxiety (Schweitzer and Rickels, 1991). Consequently, the acute anxiolytic effects of 1A agonists detected in some animal models of anxiety may be viewed as false positives. Furthermore, it is not clear whether these effects, whenever they occur, are due to stimulation of 5-HT_{1A} receptors. Indeed, a recent study has shown that the anxiolytic-like effect of the full 1A agonists 8-OH-DPAT and flesinoxan in rats under a modified Geller-Seifter conflict test was antagonized only by high doses (1.0 and/or 3.0mg/kg) of the selective 1 A antagonist WAY 100635, whereas the depressant effects of the same drugs on nonpunished responding were blocked by a much lower dose (0.1mg/kg) of WAY 100635 (King *et al., 1*997).

The aim of the present study is to investigate the role of 5-HT_{1A} receptors in the behavioral effects of 8-OH-DPAT measured in the elevated plus-maze by using the selective 1A antagonist, WAY 100135. First, a dose-effect curve for 8-OH-DPAT on indexes of anxiety and locomotion was determined. For positive control the effects of an anxiolytic dose of diazepam were measured. Finally, it was verified whether pretreatment with WAY 100135 would antagonize an effective dose of 8-OH-DPAT.

Materials and methods

Animals. Male Wistar rats weighing 200-250g were housed in glass-walled cages in groups of five, food and water freely available. Lights were on from 600h to 1800h and temperature was kept at 23±1°C.

Apparatus. The elevated plus-maze was made of wood according to the specifications of Pellow *et al.* (1985). The apparatus consisted of two opposed open arms measuring 50cm x 10cm, crossed at right angle with two opposed arms of the same size, enclosed by walls 40cm high, except for the entrance. The four arms delimited a central area of $100cm^2$. The whole apparatus was elevated 50cm above the floor. To avoid rats falling down a rim of Plexiglass 1cm high was built to surround the open arms. Illumination was provided by a 80 w light suspended 160cm above the maze. The experimental sessions were recorded by a vertically-mounted video camera linked to a TV monitor and a VCR in an adjacent room. Video tapes were later analyzed by an observer unaware of treatment conditions.

Drugs. The drugs 8-hydroxy-2-(di-n-propyl-amino)tetralin hydrobromide (8-OH-DPAT, Research Biochemicals International, Natick, MA, U.S.A.) and (+)-N-T-butyl-3-[1-[4-(2-methoxy) phenyl] piperazinyl]-1-phenylpropionanamide dihydrochloride (WAY 100135, Wyeth Research (U.K.) Ltd., Taplow, Maidenhead, U.K.) were dissolved in saline solution (0.9% NaCl) for IP and SC injection, respectively. A volume of 1 ml/kg body weight was injected.

Procedure. The experimental session was conducted either 30 min after administration of 8-OH-DPAT or 45 min after WAY 100135 injection. The rat was placed at the central square facing an enclosed arm and allowed to freely explore the elevated plus-maze for 5 min. Before the next rat was introduced, the maze was cleaned with a solution of 20% ethanol and dried. The number of entries with the four paws within the open and enclosed arms and the time spent within the open and enclosed arms were recorded. From these data, the percentage of entries onto and of time spent on open arms was calculated [100 x open / (open + enclosed)]. This parameter was considered to reflect anxiety while the number of entries into enclosed arms was used as an index of locomotion (Cruz *et al.,* 1994).

Data Analysis. The unpaired Student's-*t* test, single-factor and two-factor ANOVA followed by the Duncan multiple range test were used. A p value of 0.05 or less was required for significance.

Results

Diazepam. The dose of 2mg/kg of diazepam, given IP, significantly increased the percentage of open arm entries [$t(9) = 4.26$, $p<0.01$] and of time spent on the open arms [$t(9) = 3.55$, $p<0.01$]. The total number of entries into the enclosed arms was not significantly changed [$t(9) = 0.24$, $p>0.05$]. These results are shown in Table 1.

Table 1. Anxiolytic effect of 2.0mg/kg, IP, of diazepam on exploration of the elevated plus-maze ($p<0.01$)

Treatment	Open-arm entries (%)	Time on open arms (%)	Enclosed arm entries	N
Saline	18.1 ± 5.8	7.4 ± 5.5	5.8 ± 2.6	6
Diazepam	51.8 ± 4.4**	27.4 ± 4.9**	6.4 ± 1.4	5

Values are mean ± SE mean. ** P<0.01 compared to saline in unpaired Student's-*t* test

8-OH-DPAT. Intraperitoneal injection of 8-OH-DPAT 30 min before the experimental session affected the three maze exploration parameters. Single-factor ANOVA showed an overall drug effect on the percentage of open arm entries [$F(3,33) = 4.58$, $p = 0.009$], percentage of time spent on open arms [$F(3,33) = 6.01$, $p = 0.003$] as well as total number of enclosed arm entries [$F(3,33) = 5.38$, $p = 0.004$]. Post-hoc comparisons with the Duncan

test showed that the dose of 0.5mg/kg significantly increased each of these measures ($p<0.01$). Results are illustrated in Figure 1.

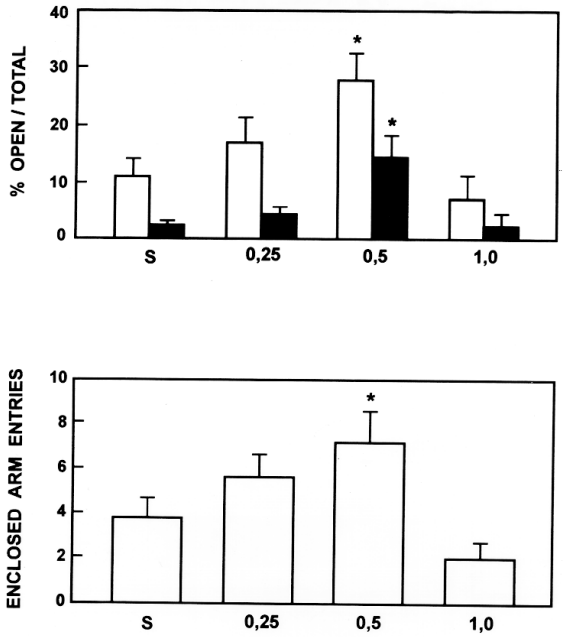

Figure 1. Effect of intraperitoneal injection of 8-OH-DPAT in rats tested in the elevated plus-maze. Data are reported as mean (SEM for 9 to 10 rats per group injected with either saline (S) or drug (0.25, 0.5 and 1.0mg/kg). The upper panel shows the percentage of entries made (open columns) and the time spent (hatched columns) in the open arms; the lower panel shows total entries in enclosed arms. One-way ANOVA showed significant effect of 0.5mg/kg dose for three analyzed parameters. ($p<0.01$ compared with saline by Duncan's test)

Combined Drug Treatment. The effects of combined treatments are illustrated in Figure 2. Consonant to the above results with single injection, 8-OH-DPAT increased the three measures of maze exploration studied when given after either vehicle or WAY 100135. WAY 100135 alone decreased the percentage of open arms entries.

On the percentage of open-arm entries, two-factor ANOVA detected a significant effect of both WAY100135 [$F(1,33) = 4.07$, $p = 0.049$] and 8-OH-DPAT [$F(1,33) = 5.46$, $p = 0.024$], but no significant interaction between the two drugs [$F(1,33) = 1.30$, $p = 0.262$]. The same analysis for the time spent on open arms showed a significant effect of 8-OH-DPAT [$F(1,33) = 4.69$, $p = 0.036$], but no effect of WAY 100135 [$F(1,33) = 1.09$, $p = 0.304$]. The interaction between the two treatments was not significant [$F(1,33) = 0.47$, $p = 0.504$]. For enclosed arms entries, there was no significant effect of WAY 100135 [$F(1,33) = 1.95$, $p = 0.169$], a significant effect of 8-OH-DPAT [$F(1,33) = 7.15$, $p = 0.011$], as well as a significant drug interaction [$F(1,33) = 9.82$, $p = 0.004$]. Further Duncan tests evidenced that the group treated with WAY 100135 plus saline differs from group treated with WAY 100135 plus 8-OH-DPAT at $p<0.01$.

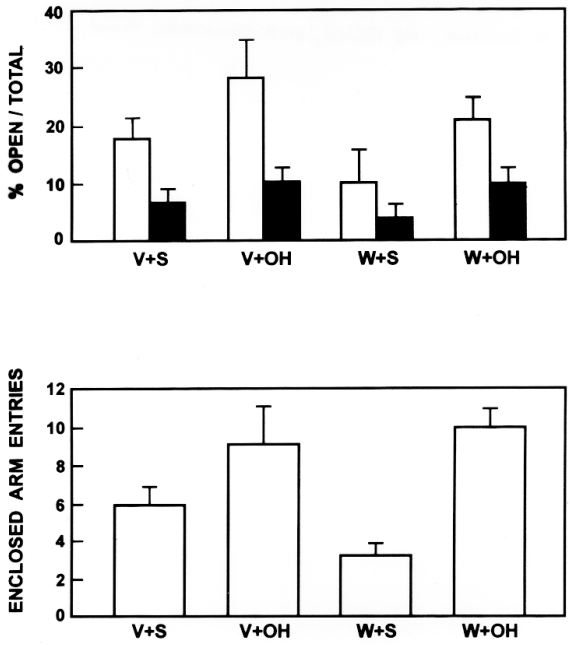

Figure 2. Effect of combined treatment of WAY100135 (W,1.0mg/kg,sc.) or vehicle (V) given before 8-OH-DPAT (OH,0.5mg/kg,ip) or saline (S) in elevated plus-maze. Columns represent mean; vertical bars represent the EPM. With regard to the percentage of open arms entries, two-way ANOVA revealed a significant effect of WAY 100135 ($p<0.05$) and 8-OH-DPAT($p<0.05$), but a non-significant interaction between the drugs ($p>0.05$). In the time spent on open arms, two way ANOVA revealed a significant effect of 8-OH-DPAT ($p<0.05$), but not of WAY 100135 ($p>0.05$) and a non-significant interaction between the drugs ($p>0.05$). For enclosed arms entries, the same test revealed a non-significant effect of WAY 100135 ($p>0.05$), a significant effect of 8-OH-DPAT($p<0.05$) and a significant interaction ($p<0.05$). Duncan's test revealed the significant difference (*$p<0.05$) between the group WAY100135 plus saline and WAY 100135 plus 8-OH-DPAT. For further specifications, see legend of Figure 1.(n= 9-10)

Discussion

Present results show that 0.5mg/kg dose of 8-OH-DPAT increased significantly the percentage of open arm entries and of time spent on open arms. Reported results with factor analysis have shown that these two measures are related to each other and selectively on the factor related to anxiety (Cruz *et al.,* 1994). Therefore, 8-OH-DPAT apparently had an anxiolytic effect in the elevated plus-maze. However, the effect was not proportional to the dose administered, since both the lower (0.25mg/kg) and the higher (1.0mg/kg) dose used were ineffective. In addition, locomotion as indicated by the number of enclosed arm entries (Cruz *et al.,* 1994) was also increased by 0.5mg/kg of 8-OH-DPAT, casting

doubt on the selectivity of the anxiolytic effect of 8-OH-DPAT. At variance with 8-OH-DPAT, 2.0mg/kg of the benzodiazepine anxiolytic diazepam affected similarly the anxiety indexes without significantly changing the number of enclosed arm entries.

Reported results about the effect of 8-OH-DPAT on the elevated plus-maze have been variable. Thus, this full agonist shows anxiogenic, null or anxiolytic effects when administered in rats (Critchley *et al.,* 1992; Moser *et al.,* 1990; Dunn *et al.,* 1989).

The same inconsistency was observed in light/dark, social interaction or open field test when 8-OH-DPAT were systemically administered in mice or rats (Olivier *et al.,* 1989; Dunn *et al.,* 1989; Kshama *et al.,* 1990, Ahlemius *et al.,* 1991).

Other full and partial 1A agonists, flesinoxan and buspirone have shown anxiolytic properties (Rodgers *et al.,* 1994; Lee and Rodgers, 1991), while several studies reveal opposite effects (Kotowski *et al.,* 1992; Moser, 1989) in elevated plus-maze.

Present results also show that the selective 5-HT_{1A} receptor blocker WAY 100135 (1.0mg/kg) administered in combination with either saline or 8-OH-DPAT decreased significantly the percentage of open arm entries, though not that of time spent on the open arms. Significance level was achieved at a borderline level of probability ($p = 0.049$). It is unlikely that WAY 100135 has an anxiogenic effect in the elevated plus-maze. In spite of this, significant decrease in locomotion caused by the combination of WAY 100135 plus saline (Figure 2) is evidencied in comparison with WAY 100135 plus 8-OH-DPAT, but not with control (vehicle plus saline).

There are evidences that by itself WAY 100135 induces a transient but significant decrease in 5-HT levels, showing partial agonist properties (Assié and Koek,1996). However, the most important fact is the failure of WAY 100135 to antagonize the anxiolytic-like and locomotor stimulant effects of 8-OH-DPAT in the elevated plus-maze shown by the present results. This lack of antagonism argues against a mediation of the behavioral effects of 8-OHDPAT through stimulation of the 5-HT_{1A} receptor.

Our results question the concept that acute anxiolytic effect of 1A agonists obtained with animal models of anxiety is due to stimulation of 5-HT_{1A} receptors. It has been argued that the anxiolytic effects of $5HT_{1A}$ receptors agonists are mediated by somatodendritics $5HT_{1A}$ receptors in the raphe nuclei (Picazo *et al.,* 1995), while the negatives effects indicate post-synaptic receptor stimulation (Jolas *et al.,* 1995; File *et al.,* 1996). The usual interpretation is that the former results point to an action on autosomic 5-HT_{1A} receptors, while the latter indicate post-synaptic receptor stimulation. Since both WAY 100135 and WAY 100635 act as antagonists on both autosomic and post-synaptic 5-HT_{1A} receptors (Przegalinski *et al.,* 1994; Forster *et al.,* 1995), the above failure of such compounds to antagonize the anxiolytic effect of full 1A agonists prompts a reexamination of such views. It should be kept in mind that the anxiolytic effect of 1A agonists reported in some animal models does not have a clinical counterpart and, thus, may be false positives in terms of predictability. Result showing that an increase in locomotion is associated with the changes in anxiety indexes argues against a genuine anxiolytic effect of 8-OH-DPAT in the elevated plus-maze. Since most animal models of anxiety rely on response disinhibition, false positive results may be generated by either a deficit in impulse control (Soubrié,1986) or non-specific motor stimulation (Tricklebank,1987).

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