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Evidence for specific involvement of 5-HT_{1A} and 5-$HT_{2A/C}$ receptors in the expression of patterns of spontaneous motor activity of the rat

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Abstract

The 5-HT_{1A} and the 5-$HT_{2A/C}$ receptor agonists 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (0.006–0.4 mg kg^{-1} s.c.) and (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (0.05–4.0 mg kg^{-1} s.c.), respectively, produced a similar stereotyped forward locomotion in rats, although the intensity of the behavioral change was considerably less with DOI. The stereotyped forward locomotion was accompanied by a slight decrease in total activity, suppression of rearing behavior and an increased activity in the periphery of the open-field arena. In support of receptor specificity, the effects of 8-OH-DPAT and DOI could be antagonised by pretreatment with the 5-$HT_{1A/B}$ and the 5-$HT_{2A/C}$ receptor antagonists (−)-pindolol (2 mg kg^{-1} s.c.) and ritanserin (2 mg kg^{-1} s.c.), respectively. In addition, (−)-pindolol, but not the selective β-adrenoceptor antagonist betaxolol, markedly enhanced the behavioral effects produced by DOI. The nature of these specific actions and interactions in terms of pre- and post-synaptic serotonergic mechanisms remains an important question.

Keywords: 5-HT receptor; Locomotor activity; Stereotyped behavior; (Rat)

1. Introduction

In a series of experiments, we have examined the effects of 5-HT_{1A} receptor agonists on patterns of spontaneous motor activity in the rat (Hillegaart et al., 1989; Ahlenius et al., 1993). Thus, systemic administration of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) or flesinoxan produces a slight decrease in total locomotor activity and a marked suppression of rearing, as recorded in an automated open-field arena (see Ahlenius et al., 1991). At the same time, the proportion of forward locomotion and locomotion in the periphery of the arena is increased. Taken together, this pattern of activity suggests a stereotyped forward locomotion along the edges of the open-field arena. Although this pattern of activity can not with certainty be linked to the 5-HT_{1A} receptor, there is strong evidence that some of its constituent parts are (Johansson and Ahlenius, 1989; Kalkman and Soar, 1990).

The present study had two objectives: (1) to examine the 8-OH-DPAT-induced stereotyped forward locomotion, as described here, in the presence of the 5-$HT_{1A/B}$ receptor blocking agent (−)-pindolol (Costain and Green, 1978; Goodwin and Green, 1985); (2) to differentiate the effects produced by the 5-HT_{1A} receptor agonist 8-OH-DPAT (Hjorth et al., 1982) from those produced by the 5-$HT_{2A/C}$ receptor agonist (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (Shannon et al., 1984). The 5-$HT_{2A/C}$ receptor antagonist ritanserin (Leysen et al., 1985) was used to confirm the specificity of DOI-induced behavioral effects in the present study. For further details on the receptor subtype specificity of these compounds see Hoyer et al. (1994).

Finally, the definition of the open-field arena by the 64 (8 × 8) photocell intersections was used to create a three-dimensional (3-D) graph of the actual distribution of activity within the open-field, in rats treated with 8-OH-DPAT or DOI.

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2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats (280–320 g) were used (B & K Universal, Sollentuna, Sweden). The animals arrived in the laboratory at least 10 days before being used in experiments and were housed, five per cage (Makrolon IV), under controlled conditions of temperature (21.0 ± 0.4°C), relative humidity (55–65%) and light-dark cycle (12 : 12 h, lights off 06.00 h). Food (R36, Ewos, Södertälje) and tap water were available ad libitum in the home cage.

2.2. Drugs

(±)-8-Hydroxy-2-(di-*n*-propylamino)tetralin HBr (8-OH-DPAT), molecular weight (MW) = 328.29 (RBI, Natick, MA, USA); (±)-1-(2,5,-dimethoxy-4-iodophenyl)-2-aminopropane HCl (DOI), MW = 357.60 (RBI); (−)-pindolol, MW = 248.33 (RBI); (±)-betaxolol, MW = 307.44 (Synthélabo, Paris, France); and ritanserin, MW = 477.57 (Janssen Pharmaceutica, Beerse, Belgium). 8-OH-DPAT, DOI and betaxolol were dissolved in physiological saline, whereas (−)-pindolol and ritanserin were dissolved in a minimal amount of glacial acetic acid and final volume made up with isotonic glucose. The controls received the corresponding vehicle. The injection route was subcutaneous, and the volume of injection was kept constant at 2 ml kg^{-1}.

2.3. Locomotor activity measurements

The spontaneous motor activity was observed in a square open-field arena (680 × 680 × 450 mm), equipped with two rows of photocells, sensitive to infrared light, placed 40 and 125 mm above the floor (Kungsbacka Mät- & Reglerteknik, Fjärås, Sweden). The distance between photocells was 90 mm, and the last photocell in a row was spaced 25 mm from the wall. The open-field was enclosed in a ventilated, sound-attenuating box with a Perspex top. Measurements were made in the dark and performed between 09.00 and 16.00 h.

The number of photocell beam interruptions was collected on a Commodore PC10-III computer, and the following variables were calculated: (i) locomotor activity (all interruptions of photo beams in the lower rows); (ii) peripheral locomotion (interruptions of photo beams provided that the beams spaced 25 mm from the wall in the lower rows also had been activated); (iii) rearing (all interruptions of photo beams in the upper rows); (iv) forward locomotion (successive interruptions of photocells in the lower rows when the animal was moving in the same direction).

Locomotor activity and rearing data were subjected to a square root transformation. Peripheral locomotion and forward locomotion are expressed as a percentage of total (non-transformed) horizontal activity. For further details of the apparatus used see Ericson et al. (1991).

2.4. Topographical analysis of locomotor activity

The software of the activity meters allowed the recording of interruptions of photocell beams at the 64 (8 × 8) intersections in the horizontal plane. From these recordings 3-D graphs were generated using the SigmaPlot software (Jandel, Erkrath, Germany).

2.5. Statistics

Statistical analysis was performed by means of a one-way analysis of variance (ANOVA), followed by

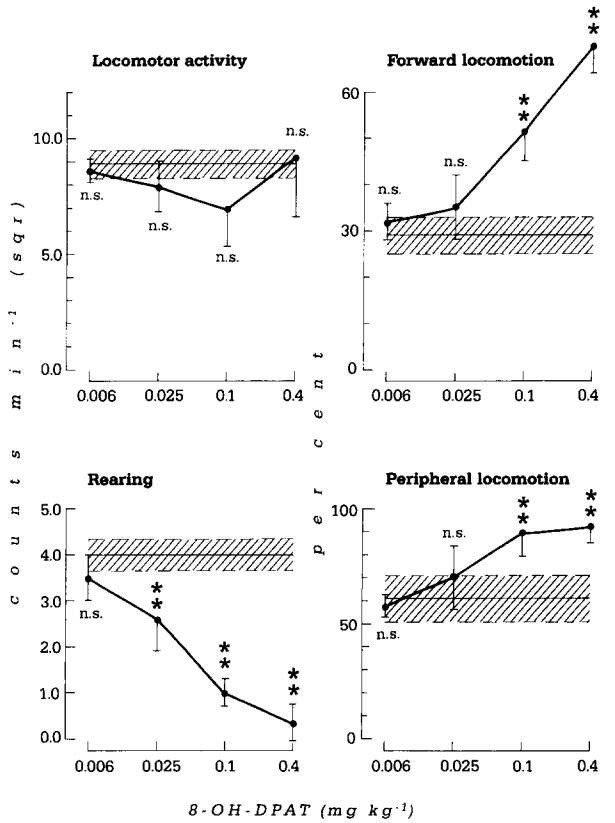

Fig. 1. Effects of 8-OH-DPAT on patterns of spontaneous motor activity of the rat. The animals were injected with 8-OH-DPAT 0.006–0.4 mg kg^{-1} s.c., 10 min prior to a 15 min test session in the activity boxes. The results are presented as means ± S.D., based on observations for 6 animals per dose. Statistical evaluation was performed by means of a one-way ANOVA, followed by the Dunnett's *t*-test for post-hoc comparisons with saline-treated controls, as shown by the shaded area. Locomotor activity: $F(4,25) = 2.29$, n.s.; Rearing: $F(4,25) = 74.34$, $P < 0.01$; Forward locomotion: $F(4,25) = 16.39$, $P < 0.01$; Peripheral locomotion: $F(4,25) = 56.19$, $P < 0.01$. $^{ns}P > 0.05$, $^{*}P < 0.05$, $^{**}P < 0.01$.

appropriate *t*-tests (Winer, 1971), as further explained in figure legends.

3. Results

3.1. Effects of 8-OH-DPAT and DOI on patterns of spontaneous motor activity of the rat

3.1.1. 8-OH-DPAT

As shown in Fig. 1, 8-OH-DPAT (0.006–0.4 mg kg^{-1}) produced the pattern of activity expected for a $5\text{-}HT_{1A}$ receptor agonist (cf. Ahlenius et al., 1991). Thus, there was a marked increase in forward locomotion along the edges of the open-field arena. At the time of the maximal effect, the animals did not rear and the total activity was unchanged in comparison with saline controls. The topography of this pattern of activity is clearly illustrated in the top graph of Fig. 3.

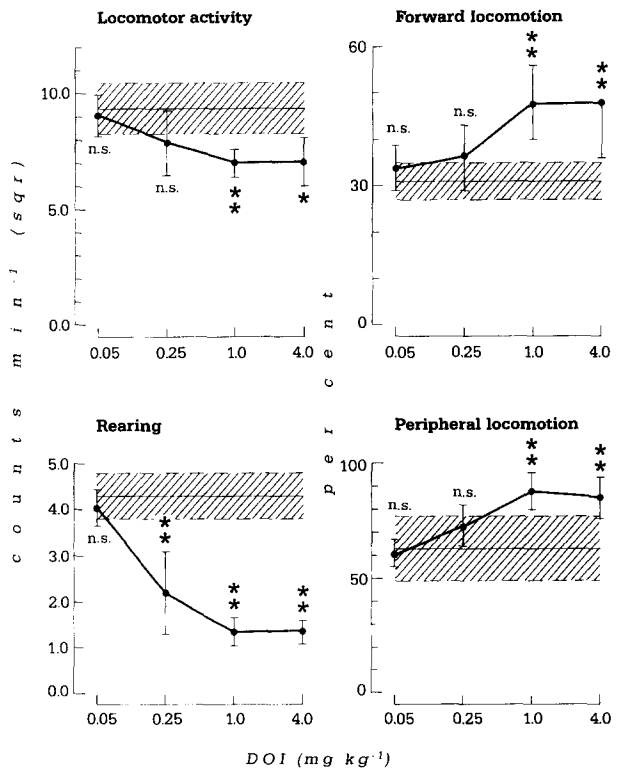

Fig. 2. Effects of DOI on patterns of spontaneous motor activity of the rat. The animals were injected with DOI 0.05–4.0 mg kg^{-1} s.c., 20 min prior to a 15 min test session in the activity boxes. The results are presented as means ± S.D., based on observations for 5 animals per dose. Statistical evaluation was performed by means of a one-way ANOVA, followed by the Dunnett's *t*-test for post-hoc comparisons with saline-treated controls, as shown by the shaded area. Locomotor activity: $F(4,20) = 5.46$, $P < 0.01$; Rearing: $F(4,20) = 37.52$, $P < 0.01$; Forward locomotion: $F(4,20) = 5.47$, $P < 0.01$; Peripheral locomotion: $F(4,20) = 8.27$, $P < 0.01$. ^{ns} $P > 0.05$, * $P < 0.05$, ** $P < 0.01$.

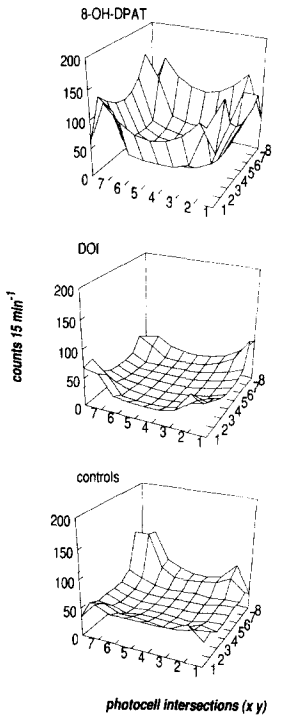

Fig. 3. Topography of locomotor activity within the open-field arena produced by the 8-OH-DPAT (0.4 mg kg^{-1}), DOI (1.0 mg kg^{-1}), and saline control treatments. The topographical map is produced by the cumulative interruptions of photocells at the 64 (8×8) intersections, as further explained in Materials and methods. The charts are based on the records of a representative control animal and of drug-treated animals at the dose producing maximal effects. The actual behavioral score (Locomotor activity, Rearing, Peripheral activity and Forward locomotion) for the animals shown in the figure were as follows: 8-OH-DPAT (11.5, 0.0, 91 and 77); DOI (7.3, 1.5, 81 and 41); Controls (8.9, 4.4, 57 and 33) (cf. Figs. 1 and 2).

3.1.2. DOI

DOI (0.05–4.0 mg kg^{-1}) produced a pattern of activity similar to that described for 8-OH-DPAT above, although the stereotyped forward locomotion was less pronounced (Fig. 2). This difference in intensity between the behavioral effects of 8-OH-DPAT and DOI was also evident from the topographical analysis of activity within the open-field, as shown in Fig. 3. As a reference, the topographical pattern of activity for a saline control rat, performing close to the mean activity score in the respective behavioral variable, is shown in the bottom graph of Fig. 3. As compared to 8-OH-DPAT- or DOI-induced behavioral changes, controls displayed an irregular pattern of activity within the open-field.

3.2. Antagonism by (−)-pindolol of 8-OH-DPAT-induced changes in spontaneous motor activity

The administration of 8-OH-DPAT (0.1 mg kg^{-1}) resulted in decreased locomotor and rearing activity, as

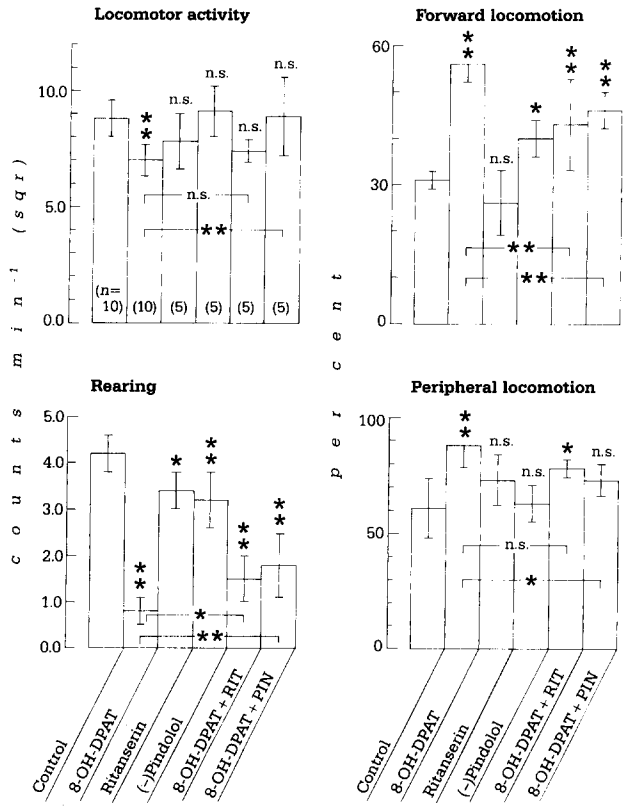

Fig. 4. Effects of ritanserin or (−)-pindolol on the effects produced by 8-OH-DPAT on spontaneous motor activity of the rat. The animals were injected with drug or saline vehicle as follows: 8-OH-DPAT 0.1 mg kg^{-1} s.c. −10 min; (−)-pindolol 2.0 mg kg^{-1} s.c. −30 min; ritanserin 2.0 mg kg^{-1} s.c. −30 min. The results are presented as means ± S.D. Statistical evaluation was performed by means of a one-way ANOVA, followed by the Dunnett's t-test for post-hoc comparisons with vehicle-treated controls, or the Student's t-test for individual comparisons as shown by brackets. Locomotor activity: $F(5,34) = 5.89$, $P < 0.01$; Rearing: $F(5,34) = 70.80$, $P < 0.01$; Forward locomotion: $F(5,34) = 32.28$, $P < 0.01$; Peripheral locomotion: $F(5,34) = 8.96$, $P < 0.01$. ^{ns} $P > 0.05$, * $P < 0.05$, ** $P < 0.01$.

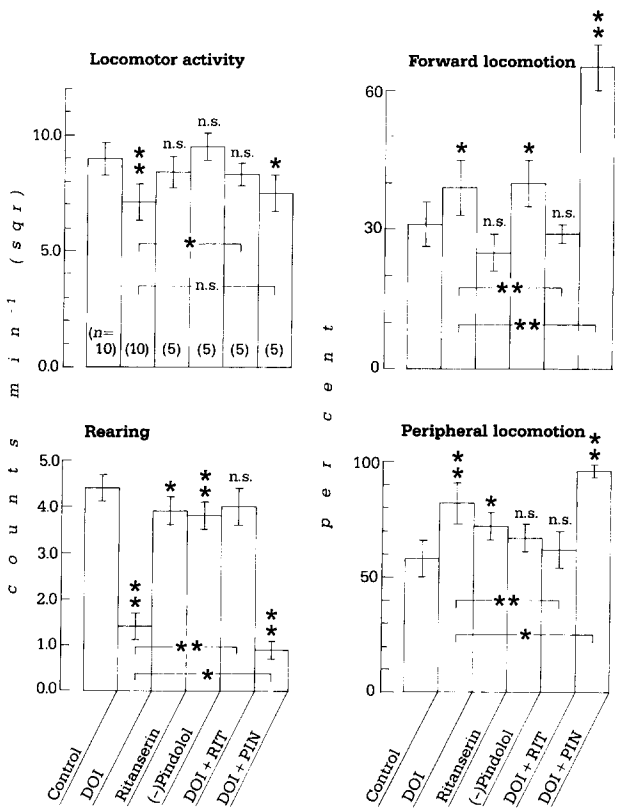

Fig. 5. Effects of ritanserin or (−)-pindolol on the effects produced by DOI on spontaneous motor activity of the rat. The animals were injected with drug or saline vehicle as follows: DOI 1 mg kg^{-1} s.c. −20 min; (−)-pindolol 2.0 mg kg^{-1} s.c. −30 min; ritanserin 2.0 mg kg^{-1} s.c. −30 min. The results are presented as means ± S.D. Statistical evaluation was performed by means of a one-way ANOVA, followed by the Dunnett's t-test for post-hoc comparisons with vehicle-treated controls, or the Student's t-test for individual comparisons as shown by brackets. Locomotor activity: $F(5,34) = 12.26$, $P < 0.01$; Rearing: $F(5,34) = 168.70$, $P < 0.01$; Forward locomotion: $F(5,34) = 41.31$, $P < 0.01$; Peripheral locomotion: $F(5,34) = 21.52$, $P < 0.01$. ^{ns} $P > 0.05$, * $P < 0.05$, ** $P < 0.01$.

well as an increased relative amount of forward and peripheral locomotion. All these effects were fully or partially restored by pretreatment with the 5-HT$_{1A}$ receptor antagonist (−)-pindolol (2 mg kg^{-1}) (Fig. 4).

It should be noted, however, that also ritanserin (2 mg kg^{-1}) partially antagonised both the 8-OH-DPAT-induced decrease in rearing and the increased forward locomotion. There were no, or only minor, effects of

Table 1
Effects of (±)-betaxolol on DOI-induced changes in the pattern of spontaneous motor activity in rats

Treatment	LMA	R	FL	PA
Saline	9.4 ± 0.5	4.6 ± 0.4	34 ± 4	54 ± 13
Betaxolol	9.0 ± 0.6 ^{ns}	4.3 ± 0.5 ^{ns}	33 ± 6 ^{ns}	66 ± 7 ^{ns}
DOI	7.9 ± 0.9 ^{a}	1.5 ± 0.9 ^{b}	53 ± 11 ^{b}	86 ± 10 ^{b}
Betaxolol + DOI	7.5 ± 0.9 ^{b}	1.3 ± 0.4 ^{b}	50 ± 2 ^{b}	81 ± 9 ^{b}

(±)-Betaxolol (4 mg kg^{-1}) and DOI (1 mg kg^{-1}) were administered s.c., 30 and 20 min before a 15 min session in the open-field arena, respectively. Locomotor activity (LMA) and rearing (R) data are expressed as mean activity min^{-1} ± S.D. (sqr), whereas the forward locomotion (FL) and peripheral activity (PA) are given as mean percent ± S.D., in relation to total LMA (see Materials and methods for further details). Statistical analysis ($n = 5$ per group) was performed by means of a one-way ANOVA, followed by the Dunnett's t-test for comparisons with saline-treated controls, as shown in the Table. $F(3,16) = 7.10$, 45.43, 11.73 and 9.99 for LMA, R, FL and PA, respectively. $P < 0.01$ in all cases. ^{ns} $P > 0.05$, ^{a} $P < 0.05$, ^{b} $P < 0.01$.

(−)-pindolol or ritanserin by themselves on the various components of the spontaneous motor activity (Fig. 4).

3.3. Antagonism by ritanserin of DOI-induced changes in spontaneous motor activity

There were statistically significant effects of DOI (1 mg kg^{-1}) on all aspects of the spontaneous motor activity. Ritanserin pretreatment (2 mg kg^{-1}) fully restored these DOI-induced behavioral effects (Fig. 5). With the exception of locomotor activity, pretreatment with (−)-pindolol (2 mg kg^{-1}) produced a statistically significant enhancement of the effects produced by DOI (Fig. 5). These latter effects are in all probability not related to the β-adrenoceptor blocking properties of (−)-pindolol since the selective β-adrenoceptor antagonist (±)-betaxolol (4 mg kg^{-1} s.c.) was totally ineffective in this regard. Thus, the Student's *t*-test gave *t*-values of 0.89 ($P > 0.05$), or less, for all comparisons between the different items of spontaneous motor activity displayed by DOI- and betaxolol + DOI-treated animals. Betaxolol by itself did not affect the spontaneous motor activity (Table 1).

4. Discussion

There have been reports that 8-OH-DPAT can produce both an increased (Tricklebank et al., 1984; Kalkman and Soar, 1990) and decreased (Hillegaart et al., 1989; Mittman and Geyer, 1989) spontaneous motor activity in rats. The induction of stereotyped forward locomotion by 8-OH-DPAT provides a good explanation for the different results reported, although other factors, such as time after administration and degree of habituation, may also influence the quality of effect obtained (Evenden and Ängeby-Möller, 1990). This stereotyped forward locomotion is accompanied by a decrease in total locomotor activity, loss of rearing, and an increase in relative activity in the periphery of the open-field arena, as shown in the present and previous reports from this laboratory (Ahlenius et al., 1991, 1993). This interpretation of the recorded pattern of behavioral effects receives strong support from the 3-D topographical analysis, as shown in Fig. 3.

All the various aspects of the stereotyped forward locomotion induced by the 5-HT_{1A} receptor agonist, as observed here, were antagonised by pretreatment with the 5-$HT_{1A/B}$ receptor antagonist (−)-pindolol, supporting an important role of the 5-HT_{1A} receptor in the effects produced by 8-OH-DPAT. The administration of DOI resulted in a similar, but less pronounced, stereotyped pattern of activity within the open-field, and this effect was in all probability mediated via 5-$HT_{2A/C}$ receptors, since it was effectively antagonised by pretreatment with ritanserin, which has high affinity for these 5-HT receptor subtypes.

It is interesting to note that the suppression of rearing and the increase in forward locomotion produced by 8-OH-DPAT in the present study also were partially antagonised by ritanserin, suggesting that the 5-$HT_{2A/C}$ receptor, to some extent, may be involved in the effects of 8-OH-DPAT on spontaneous motor activity in the rat. More remarkable was the interaction between (−)-pindolol and DOI. All aspects of DOI-induced effects on the spontaneous motor activity, except for the suppression of locomotor activity, were enhanced by (−)-pindolol treatment. This enhancement of the DOI-induced behavioral changes is in all probability related to the 5-HT_1 receptor blocking properties of (−)-pindolol, since the selective β-adrenoceptor antagonist betaxolol (Cavero et al., 1983) was ineffective in this regard. Thus, β-adrenoceptor antagonist properties are not involved in the effects of (−)-pindolol in a manner analogous to the behavioral stimulation reported by some investigators when combining β-adrenoceptor antagonists with 5-HT_{1A} receptor agonists (Tricklebank et al., 1984; Kalkman, 1989). It should also be noted that under the present conditions (−)-pindolol is an effective antagonist of 8-OH-DPAT-induced effects on spontaneous motor activity in the rat.

Relevant to the present observations of synergy between the 5HT_{1A} receptor antagonist and the 5-$HT_{2A/C}$ receptor agonist, the DOI-induced suppression of male rat sexual behavior, which is fully restored by ritanserin, has been found to be further suppressed by treatment with (−)-alprenolol (Klint et al., 1992). This also applies to suppression of male rat sexual behavior by 5-hydroxytryptophan (5-HTP), where the behavioral suppression is markedly enhanced by (−)-pindolol pretreatment (Ahlenius and Larsson, 1991). Furthermore, the interactions between (−)-pindolol and DOI, as observed here, have a counterpart in the effects of 8-OH-DPAT on 5-HT_2 receptor agonist-induced head-shakes in rats. Thus, the 5-HT_{1A} receptor agonist has been reported to antagonise the head-shakes produced by quipazine or DOI, and this effect is disinhibited by (−)-pindolol pretreatment (Yocca et al., 1990; Albinsson et al., 1994). Also the enhancement of 5-HTP-induced suppression of male rat sexual behavior, as mentioned above, is mirrored by a dose-dependent antagonism of the 5-HTP-induced effects by 8-OH-DPAT treatment (Ahlenius and Larsson, 1985).

In recent reports it has been shown that 5-HT_{1A} receptor blockade, presumably of serotonergic autoreceptors, promotes the ability of serotonin re-uptake inhibitors to release forebrain 5-HT in the rat (Invernizzi et al., 1992; Hjorth, 1993). This interaction has been explained by assuming that the 5-HT_{1A} receptor blocking agent prevents autoreceptor-mediated inhibi-

tion of release and firing in serotonergic neurones elicited by the re-uptake inhibitor, thereby resulting in a disinhibition of serotonergic neurotransmission and an enhanced activity at postsynaptic 5-HT receptors (other than 5-HT_{1A}) (see Artigas, 1993). Since brain 5-$HT_{2A/C}$ receptors are primarily found in the forebrain, the observation that the DOI-induced behavioral effects could be enhanced by a 5-HT_{1A} receptor antagonist suggests that (−)-pindolol disinhibits firing and release in serotonergic neurones tonically inhibited by the endogenous neurotransmitter. The fact, however, that there is only weak evidence for the operation of such feedback inhibition (Bedard et al., 1972; Carlsson and Lindqvist, 1972), together with the present findings, leaves the possibility that some of the 5-HT_{1A}/5-$HT_{2A/C}$ receptor interactions may occur postsynaptically.

In conclusion: the administration of 8-OH-DPAT and DOI resulted in both cases in stereotyped forward locomotion in rats. This effect, which is most conspicuous for 8-OH-DPAT, is sensitive to (−)-pindolol and ritanserin, suggesting a specific role for both the 5-HT_{1A} and the 5-$HT_{2A/C}$ receptors in the mediation of spontaneous motor activity in the rat. Finally, whereas ritanserin only marginally affected 8-OH-DPAT-induced stereotyped forward locomotion, (−)-pindolol pretreatment markedly enhanced the DOI-induced behavioral effects. Considering the distribution of brain 5-HT_{1A} and 5-$HT_{2A/C}$ receptors, these latter interactions may, at least partially, be postsynaptic in origin.

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