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# Behavioural evidence for a functional interaction between central 5-$HT_2$ and 5-$HT_{1A}$ receptors

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1 The possibility of 5-$HT_2$ receptor modulation of central 5-$HT_{1A}$ receptor function has been examined using the 5-hydroxytryptamine (5-HT) behavioural syndrome induced by 5-$HT_{1A}$ receptor active drugs in rats.

2 The 5-$HT_2$/5-$HT_{IC}$ antagonist ritanserin (0.1–2 mg $kg^{-1}$) increased the 5-HT behavioural syndrome induced by submaximally effective doses of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) and gepirone.

3 Pretreatment with the 5-$HT_2$/5-$HT_{1C}$ antagonist ICI 170,809 (0.25–5 mg $kg^{-1}$) also enhanced the behavioural syndrome induced by 8-OH-DPAT or 5-MeODMT.

4 The 5-$HT_2$/$\alpha_1$-adrenoceptor antagonist ketanserin in a low dose (0.25 mg $kg^{-1}$) significantly increased the 5-HT behavioural syndrome induced by 8-OH-DPAT or 5-MeODMT, while in a higher dose (2.5 mg $kg^{-1}$) this drug decreased the response. Experiments with prazosin indicate that the higher dose of ketanserin might reduce the 5-HT behavioural syndrome through blockade of $\alpha_1$-adrenoceptors.

5 Ritanserin and ICI 170,809 had no effect on apomorphine-induced stereotypy or hyperactivity, indicating that these drugs do not produce non-specific behavioural activation.

6 Ritanserin and ICI 170,809 inhibited quipazine-induced wet dog shakes at doses similar to those enhancing the 5-HT behavioural syndrome.

7 We suggest that ritanserin, ICI 170,809 and ketanserin enhance 5-$HT_{1A}$ agonist-induced behaviour through blockade of an inhibitory 5-$HT_2$ receptor regulating or coupled to 5-$HT_{1A}$ receptor-mediated function.

## Introduction

5-Hydroxytryptamine (5-HT) receptors in the central nervous system are currently classified into three broad categories, 5-$HT_1$, 5-$HT_2$ and 5-$HT_3$ (Peroutka & Snyder, 1979; Bradley *et al.*, 1986; Kilpatrick *et al.*, 1987). Further, 5-$HT_1$ receptors have been subdivided into 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{1C}$ and 5-$HT_{1D}$ subtypes (Pedigo *et al.*, 1981; Pazos *et al.*, 1984; Herrick-Davis & Titeler, 1988).

A number of drugs showing selectivity for the 5-$HT_1$ receptor sub-types exist. In particular, several compounds with both high affinity and selectivity for the 5-$HT_{1A}$ receptor have been identified. These include 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetralin) and gepirone, both of which have an affinity ($K_i$ in the nM range) for the 5-$HT_{1A}$ binding site in rat brain membranes which exceeds by several orders of magnitude their affinity for either the 5-$HT_{1B}$, 5-$HT_{1C}$, 5-$HT_{1D}$ or 5-$HT_2$ recognition sites (Middlemiss & Fozard, 1983; Peroutka, 1985; Hoyer, 1988a). The classical 5-HT agonist 5-MeODMT (5-methoxy-N,N-dimethyltryptamine) displays high affinity for the 5-$HT_{1A}$ binding site with somewhat less affinity for the 5-$HT_{1B}$, 5-$HT_{1C}$ and 5-$HT_{1D}$ binding sites (Sills *et al.*, 1984; Hoyer, 1988a).

Administration of 8-OH-DPAT (Hjorth *et al.*, 1982), gepirone (Eison *et al.*, 1986) or 5-MeODMT (Grahame-Smith, 1971) to rats results in a complex behavioural syndrome similar to the behaviour seen following administration of 5-HT precursors or 5-HT releasers (see, for example, Grahame-Smith, 1971; Green & Grahame-Smith, 1974; Jacobs, 1976). The fact that the behavioural syndrome induced by 8-OH-DPAT and 5-MeODMT is, firstly, antagonized by pindolol and propranolol stereoselectively and by other compounds with high affinity for the 5-$HT_{1A}$ site (Lucki *et al.*, 1984; Tricklebank *et al.*, 1984; 1985; Sharp *et al.*, 1990) and, secondly, unchanged by lesion of 5-HT neurones or inhibition of 5-HT synthesis (Trulson *et al.*, 1976; Deakin & Green, 1978; Hjorth *et al.*, 1982; Tricklebank *et al.*, 1984), argues strongly for the involvement of postsynaptic 5-$HT_{1A}$ receptors in the 5-HT behavioural syndrome.

Previously, Goodwin & Green (1985) found that pretreatment with ritanserin enhanced hyperactivity in rats induced by the 5-$HT_1$ agonist RU 24969 and, on the basis of the then known 5-$HT_2$ antagonist properties of ritanserin (Leysen *et al.*, 1985; Colpaert *et al.*, 1985), suggested that there might be a functional interaction between central 5-$HT_2$ and 5-$HT_1$ receptors. However, it is now recognised that ritanserin only has a slightly greater selectivity for 5-$HT_2$ than 5-$HT_{1C}$ binding sites (Hoyer, 1988a,b). This is also the case for the recently developed, potent 5-$HT_2$ antagonist, IC 170,809 (Blackburn *et al.*, 1988; Blackburn personal communication). On the other hand, ketanserin has been shown to have 70 fold greater affinity for 5-$HT_2$ versus 5-$HT_{1C}$ binding sites (Hoyer, 1988a). This study investigated the effects of ritanserin, ICI 170,809 and ketanserin on the 5-HT behavioural syndrome induced in rats by drugs active at 5-$HT_{1A}$ receptors.

## Methods

### *Animals*

Albino male Sprague-Dawley rats, 200–250 g, (Harlan Olac, Bicester, U.K.) were housed at the department for at least one week before being used in the experiments. Animals were kept in groups of 6–7 under conditions of controlled temperature (21 ± 1°C) and lighting (dark period 19 h 00 min–7 h 00 min) with free access to food and water. All experiments were performed during the light phase of the cycle between 10 h 00 min and 16 h 00 min.

### *Behavioural observations*

For measurement of the 5-HT behavioural syndrome, rats were placed in individual clear Plexiglass cages with a layer of

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sawdust covering the bottom, five to ten minutes before drug administration. Individual components of the syndrome (head weaving, forepaw treading, hind limb abduction, flat body posture) were scored during observation periods of 45 s per rat on a 4-point ranked intensity scale (0 = absent, 1 = equivocal, 2 = definite, 3 = extreme: Deakin & Green, 1978). For experiments with 8-OH-DPAT and gepirone, observations were made every 10 min for 60 min. In the case of 5-MeODMT, observations were made every 5 min for 30 min. Scores for each component were summed over the 6 observation periods. Total behavioural scores were obtained by summing the scores of each component. Vehicle or 5-HT antagonists were injected 30 min before the 5-HT agonists. For all the behavioural studies, the rating observer was blind to the pretreatment conditions.

Apomorphine-induced stereotypy was rated using the scale of Creese & Iversen (1973): 0 = asleep or inactive; 1 = episodes of normal activities; 2 = discontinuous activity with bursts of prominent sniffing and rearing; 3 = continuous stereotyped sniffing or rearing along a fixed path; 4 = stereotyped sniffing or rearing fixated in one location; 5 = stereotyped behaviour with bursts of licking or gnawing; 6 = continuous licking or gnawing. The ratings were assigned during 45 s observation periods at 5 min intervals for 30 min. Scores were summed for the 6 observation periods. Apomorphine-induced behavioural activation was also measured by Columbus Instrument Opto-Varimex II Activity Monitors (Linton Instruments, Sheffield, U.K.). Rats were placed singly in clear Plexiglass cages positioned between a row of 15 photocells. Animals were allowed to habituate to the cages for 30 min before drug administration. Results were collected for 30 min following apomorphine administration.

To measure wet dog shake behaviour, rats were placed singly in clear Plexiglass cages 5–10 min before drug administration. The number of wet dog shakes was counted over 40 min after administration of quipazine, according to the procedure of Vetulani *et al.* (1980). Wet dog shakes were characterized as rapid side to side twitches of the head and ears, as previously described (Bedard & Pycock, 1977).

### *Drugs*

Drugs were obtained from the following sources: apomorphine hydrochloride (Macfarlan Smith Ltd, Edinburgh, U.K.); 2-(2-dimethylaminopropylthio)-3-phenylquinoline hydrochloride (ICI 170,809); gepirone hydrochloride (Bristol Meyers, Evansville, IN, U.S.A.); haloperidol (Janssen Pharmaceutica, Beerse, Belgium); 8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide (8-OH-DPAT; Research Biochemicals Inc., Semat, St. Albans, U.K.); ketanserin tartrate (Janssen Pharmaceutica, Beerse, Belgium); 5-methoxy-N,N-dimethyltryptamine hydrochloride (5-MeODMT; Sigma Chemical Co., Poole, U.K.); prazosin hydrochloride (Sigma Chemical Co., Poole, U.K.); quipazine maleate (Research Biochemicals Inc., Semat, St. Albans, U.K.); ritanserin tartarate (Janssen Pharmaceutica, Beerse, Belgium). Haloperidol was used as the commercially available solution Haldol (5 mg ml$^{-1}$) diluted with 0.9% NaCl. ICI 170,809, ketanserin, prazosin and ritanserin were dissolved in a few drops of glacial acetic acid and then diluted to volume with 5% glucose. All other drugs were dissolved directly in 0.9% NaCl solution. Drugs were injected subcutaneously (s.c.) in a volume of 2 ml kg$^{-1}$.

### *Statistics*

Observer scores for the 5-HT behavioural syndrome, apomorphine-induced stereotypy and quipazine-induced wet dog shakes are presented as median values and statistical comparisons were made with the Mann Whitney U test preceded by the Kruskal Wallis test where appropriate. Activity meter counts are presented as mean values and were analysed by Student's *t* test.

## Results

### *Behavioural effects of 8-OH-DPAT, 5-MeODMT and gepirone in untreated rats*

8-OH-DPAT (0.1–5 mg kg$^{-1}$ s.c.) dose-dependently induced the 5-HT behavioural syndrome, as evident by the presence of head weaving, reciprocal forepaw treading, hindlimb abduction and flat body posture (Figure 1a). The onset of these behaviours occurred within 10 min of 8-OH-DPAT administration. From the dose-response data, a submaximally effective dose of 8-OH-DPAT of 0.75 mg kg$^{-1}$ was chosen for subsequent experiments.

5-MeODMT (1–10 mg kg$^{-1}$ s.c.) also dose-dependently produced the four scored behaviours which occurred within 5 min of 5-MeODMT administration (Figure 1b). For further experiments a submaximally effective dose of 5-MeODMT of 2 mg kg$^{-1}$ was chosen. Finally, gepirone (5–100 mg kg$^{-1}$ s.c.) dose-dependently produced head weaving, reciprocal forepaw

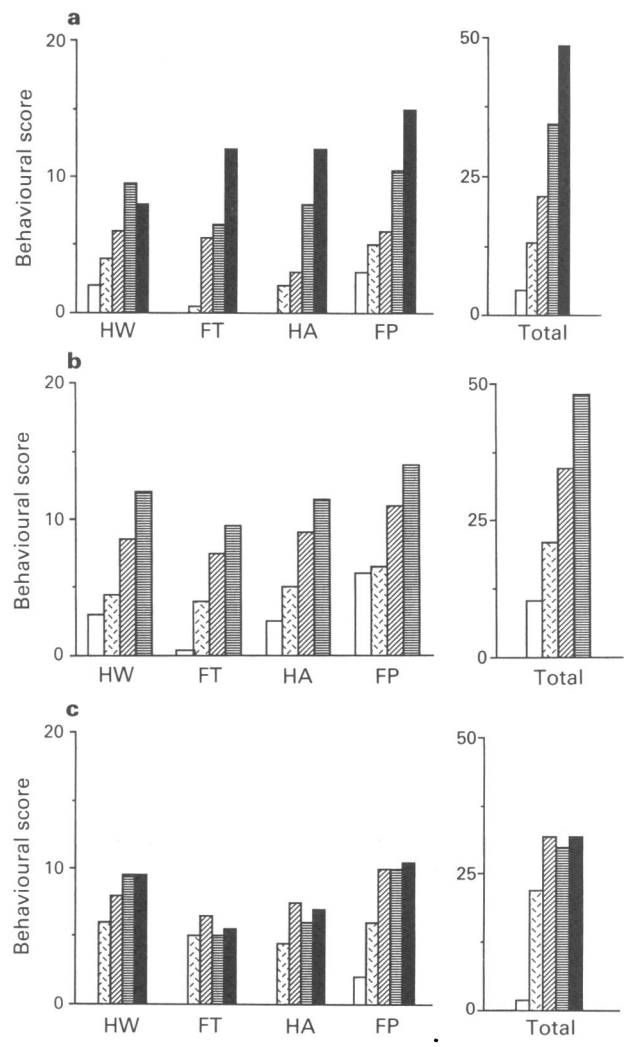


**Figure 1** Dose-response effect of the 5-hydroxytryptamine (5-HT) agonists on behaviour in the rat. The columns represent the median accumulated score of components of the 5-HT behavioural syndrome (HW – head weaving, FT – forepaw treading, HA – hindlimb abduction, FP – flat body posture, Total – total behavioural score). (a) 8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), 0.1 (open columns), 0.25 (stippled), 0.75 (diagonally hatched), 1.5 (horizontally hatched), 3.0 (solid) mg kg$^{-1}$. (b) 5-Methoxy-N,N-dimethyltryptamine (5-MeODMT), 1.0 (open columns), 2.0 (stippled), 5.0 (diagonally hatched), 10.0 (horizontally hatched) mg kg$^{-1}$. (c) Gepirone, 5.0 (open columns), 10.0 (stippled), 25.0 (diagonally hatched), 50.0 (horizontally hatched), 100.0 (solid) mg kg$^{-1}$. $n$ = 6 rats per dose. See Methods for details of the scoring procedure.

treading, hindlimb abduction and flat body posture (Figure 1c). For further experiments, a submaximally effective dose of 10 mg kg$^{-1}$ was chosen.

### *Effect of ritanserin on the 8-OH-DPAT-, 5-MeODMT- and gepirone-induced 5-HT behavioural syndrome*

Pretreatment with ritanserin (0.1–2 mg kg$^{-1}$ s.c.) dose-dependently increased head weaving, forepaw treading, hindlimb abduction and flat body posture induced by 8-OH-DPAT 0.75 mg kg$^{-1}$ s.c. (Figure 2). Enhancement of 8-OH-DPAT-induced behaviour by ritanserin was also evident from the total behavioural score. The effect of ritanserin was evident at 0.1 mg kg$^{-1}$ and maximal at 0.4 mg kg$^{-1}$.

Ritanserin pretreatment (0.1–0.4 mg kg$^{-1}$ s.c.) also dose-dependently increased 5-MeODMT-elicited (2 mg kg$^{-1}$ s.c.) head weaving, forepaw treading, hindlimb abduction and flat posture (Figure 3).

Pretreatment with ritanserin (0.2 mg kg$^{-1}$ s.c.) before gepirone (10 mg kg$^{-1}$ s.c.) significantly increased the total syndrome score as well as the four component scores summed over 60 min (Figure 4).

The dose-response curves for each of the component behaviours and the total syndrome score produced by 8-OH-DPAT (0.1–3 mg kg$^{-1}$ s.c.) were shifted to the left by ritanserin pretreatment (0.2 mg kg$^{-1}$ s.c.) (Figure 5). Ritanserin pretreatment reduced the estimated $ED_{50}$ for 8-OH-DPAT induction

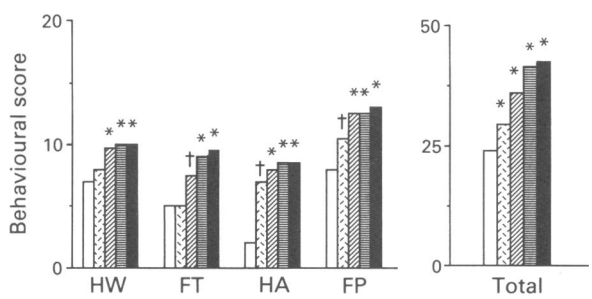


**Figure 2** Effect of pretreatment with various doses of ritanserin on components of the 5-hydroxytryptamine (5-HT) behavioural syndrome induced in rats by 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, 0.75 mg kg$^{-1}$). Each column represents the median accumulated behavioural score of rats pretreated with either vehicle (open columns) or ritanserin at doses of 0.1 (stippled), 0.2 (diagonally hatched), 0.4 (horizontally hatched) or 2.0 (solid) mg kg$^{-1}$. $n = 6$ for each treatment group. $n = 24$ for the vehicle-treated group. †$P < 0.05$, *$P < 0.01$ compared with 6 vehicle controls tested concurrently. See legend to Figure 1 for key to abbreviations.

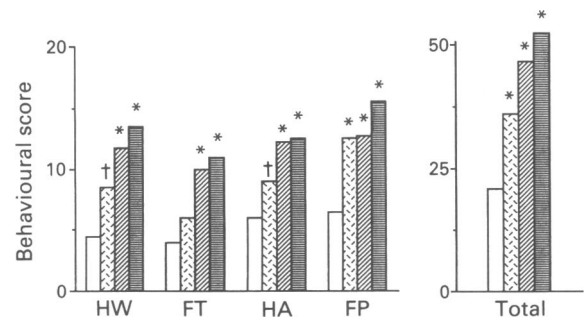


**Figure 3** Effect of pretreatment with various doses of ritanserin on components of the 5-hydroxytryptamine (5-HT) behavioural syndrome induced in rats by 5-methoxy-N-N-dimethyltryptamine (5-MeODMT, 2 mg kg$^{-1}$). Each column represents the median accumulated behavioural score of rats pretreated with either vehicle (open columns) or ritanserin at doses 0.1 (stippled), 0.2 (diagonally hatched), or 0.4 (horizontally hatched) mg kg$^{-1}$. $n = 6$ for each treatment group; $n = 18$ for the vehicle-treated group. †$P < 0.05$, *$P < 0.01$ compared with 6 vehicle controls tested concurrently. See legend to Figure 1 for key to abbreviations.

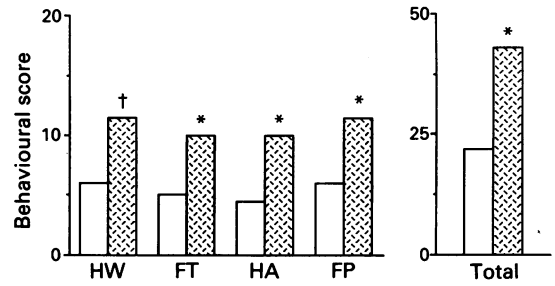


**Figure 4** Effect of pretreatment with ritanserin on components of the 5-hydroxytryptamine (5-HT) behavioural syndrome induced in rats by gepirone (10 mg kg$^{-1}$). Each column represents the median accumulated behavioural score of rats pretreated with either vehicle (open columns) or 0.2 mg kg$^{-1}$ ritanserin (stippled columns). $n = 6$ for the vehicle and treatment groups. †$P < 0.05$, *$P < 0.01$ compared with controls tested concurrently. See legend to Figure 1 for key to abbreviations.

of the 5-HT behavioural syndrome from 0.92 mg kg$^{-1}$ to 0.42 mg kg$^{-1}$.

Ritanserin pretreatment (2 mg kg$^{-1}$ s.c.) before a saline injection did not produce any components of the 5-HT behavioural syndrome when scored for 60 min (data not shown).

### *Effect of ICI 170,809 on the 8-OH-DPAT- and 5-MeODMT-induced 5-HT behavioural syndrome*

Pretreatment with ICI 170,809 (0.25–5 mg kg$^{-1}$ s.c.) before 8-OH-DPAT (0.75 mg kg$^{-1}$ s.c.) dose-dependently potentiated head weaving, forepaw treading, hindlimb abduction and flat body posture (Figure 6). All tested doses of ICI 170,809 significantly increased the total 5-HT behavioural syndrome score for the 60 min trial.

Pretreatment with ICI 170,809 (5 mg kg$^{-1}$ s.c.) caused an enhancement of head weaving and forepaw treading induced

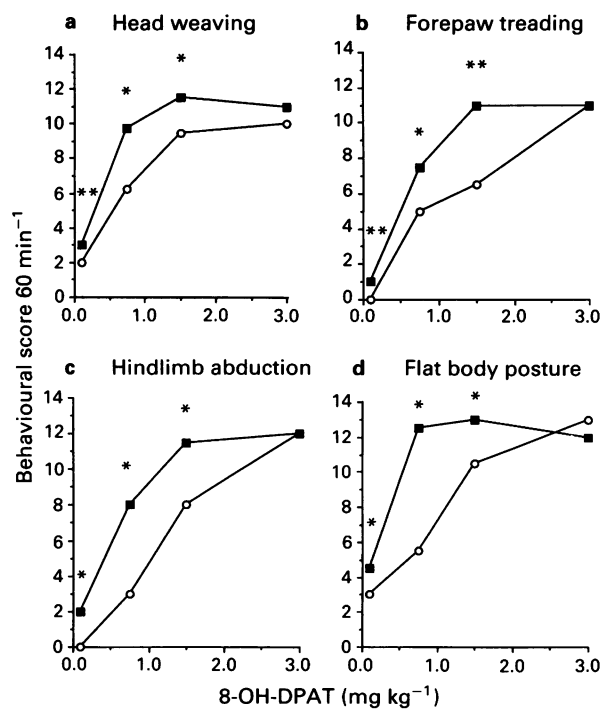


**Figure 5** Effect of ritanserin on the 5-hydroxytryptamine (5-HT) behavioural syndrome dose-response curve to 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) in rats. 8-OH-DPAT was injected to rats pretreated with either vehicle (○) or ritanserin 0.2 mg kg$^{-1}$ (■). Each point represents the median accumulated behavioural score obtained from a group of 6 rats. *$P < 0.05$, **$P < 0.01$ compared with controls tested concurrently.

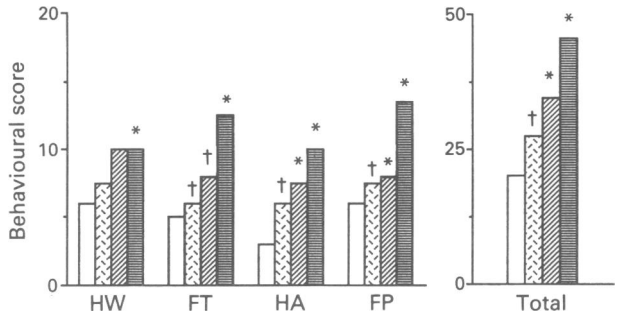


**Figure 6** Effect of pretreatment with various doses of ICI 170,809 on components of the 5-hydroxytryptamine (5-HT) behavioural syndrome induced in rats by 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, 0.75 mg kg$^{-1}$). Each column represents the median accumulated behavioural score of rats pretreated with either vehicle (open columns) or ICI 170,809 at 0.25 (stippled), 1.0 (diagonally hatched), or 5.0 (horizontally hatched) mg kg$^{-1}$. $n = 6$ for each treatment group; $n = 18$ for the vehicle-treated group. † $P < 0.05$, * $P < 0.01$ compared with the 6 vehicle controls tested concurrently. See legend to Figure 1 for key to abbreviations.

by 2 mg kg$^{-1}$ 5-MeODMT (Figure 7). In this experiment, hindlimb abduction and flat body posture tended to increase but the change did not reach statistical significance ($P < 0.075$). However, the total behavioural score was significantly increased.

Pretreatment with ICI 170,809 (5 mg kg$^{-1}$ s.c.) before saline administration did not produce any components of the 5-HT behavioural syndrome when scored for 60 min (data not shown).

### *Effect of ketanserin on the 8-OH-DPAT- and 5-MeODMT-induced 5-HT behavioural syndrome*

As shown in Figure 8a pretreatment with low and high doses of ketanserin (0.25 and 2.5 mg kg$^{-1}$ s.c.) had different effects on the 5-HT behavioural syndrome induced by 8-OH-DPAT (0.75 mg kg$^{-1}$ s.c.). At the lower dose, ketanserin significantly ($P < 0.05$) increased 8-OH-DPAT-induced hindlimb abduction, flat body posture and total syndrome score and also tended to augment headweaving and forepaw treading ($P < 0.1$). At the higher dose, ketanserin tended to reduce all four behavioural components.

Pretreatment with low and high doses of ketanserin (0.25 and 2.5 mg kg$^{-1}$ s.c.) also had a differential effect on the 5-HT behavioural syndrome when induced by 5-MeODMT (2 mg kg$^{-1}$ s.c.) (Figure 8b). At the lower dose, ketanserin significantly increased the hindlimb abduction, flat body posture

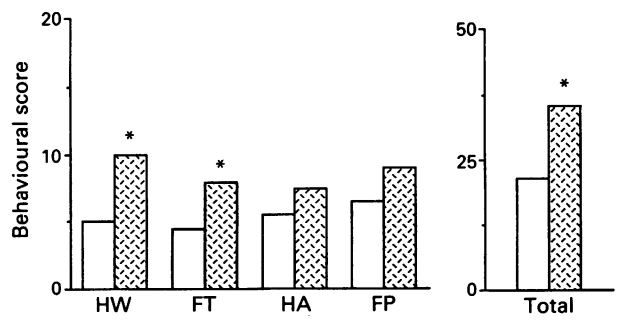


**Figure 7** Effect of pretreatment with ICI 170,809 (5 mg kg$^{-1}$) on components of the 5-hydroxytryptamine (5-HT) behavioural syndrome induced in rats by 5-methoxy-N,N-dimethyltryptamine (5-MeODMT, 2 mg kg$^{-1}$). Each column represents the median accumulated behavioural score of rats pretreated with either vehicle (open columns) or ICI 170,809 (stippled columns). $n = 6$ for each treatment group; $n = 12$ for the vehicle-treated group. * $P < 0.01$ compared with the 6 vehicle controls tested concurrently. See legend to Figure 1 for key to abbreviations.

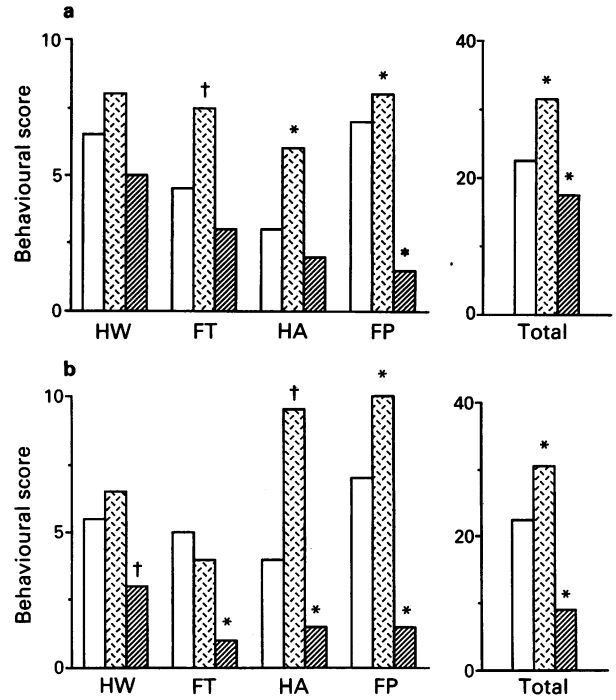


**Figure 8** Effect of pretreatment with ketanserin on the 5-hydroxytryptamine (5-HT) behavioural syndrome induced by either (a) 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, 0.75 mg kg$^{-1}$) or (b) 5-methoxy-N,N-dimethyltryptamine (5-MeODMT, 2 mg kg$^{-1}$). Each column represents the median accumulated behavioural score of rats pretreated with either vehicle (open columns) or ketanserin at 0.25 (stippled) or 2.5 (diagonally hatched) mg kg$^{-1}$. $n = 6$ for each treatment group; $n = 12$ for the vehicle-treated groups. † $P < 0.05$, * $P < 0.01$ compared with the 6 vehicle controls tested concurrently. See legend to Figure 1 for key to abbreviations.

and total syndrome score. At the higher dose, ketanserin significantly decreased all the components except hindlimb abduction.

### *Effect of haloperidol on the 8-OH-DPAT-induced behavioural syndrome*

Haloperidol (0.25 mg kg$^{-1}$ s.c.) abolished head weaving (HW) and forepaw treading (FT) induced by 8-OH-DPAT (0.75 mg kg$^{-1}$ s.c.). This dose of haloperidol significantly increased ($P < 0.05$) hindlimb abduction (HA) and flat body posture (FP) (control median values [inter quartile range]: HW 6[−0, +1], FT 5 [−0, +0], HA 2.5 [−0.5, +0.5], FP 7 [−1, +1], total score 20.5 [−1.5, +1.5] haloperidol: HW 0 [−0, +0], HA 9 [−4, +7], FP 16 [−2, +1], total score 24 [−4, +9]).

### *Effect of prazosin on 8-OH-DPAT-induced behavioural syndrome*

Prazosin (1 mg kg$^{-1}$ s.c.) virtually abolished head weaving and forepaw treading induced by 8-OH-DPAT (0.75 mg kg$^{-1}$ s.c.). At the same time, prazosin significantly ($P < 0.05$) increased hindlimb abduction and flat body posture (control: HW 6.5 [−1.5, +0.5], FT 5 [−0, +1], HA 2 [−1, +0], FP 7 [−1, +1], total score 20.5 [−0.5, +0.5] prazosin: HW 0.5 [−0.5, +1.5], FT 0 [−0, +0], HA 12.5 [−0.5, +1.5], FP 12 [−1, +2], total score 26 [−2, +2]).

### *Effect of ritanserin and ICI 170,809 on the behavioural response to apomorphine*

Pretreatment (30 min) with ritanserin (0.4 and 2 mg kg$^{-1}$ s.c.) or ICI 170,809 (10 mg kg$^{-1}$ s.c.) had no effect on stereotypy or

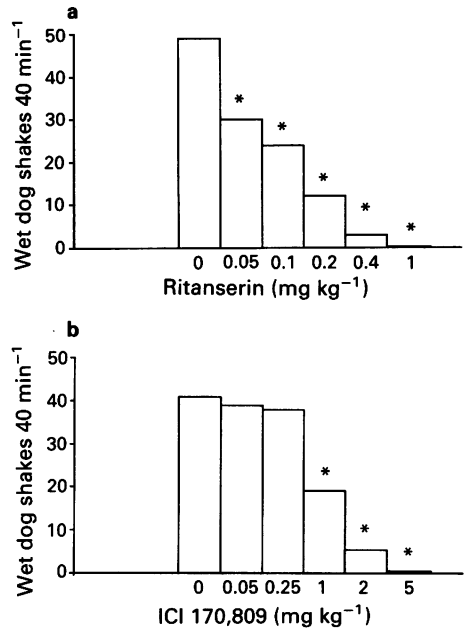


**Figure 9** Effect of ritanserin (a) and ICI 170,809 (b) on quipazine-induced wet dog shake behaviour in the rat. Each column represents the median number of wet dog shakes induced over 40 min by 5 mg kg$^{-1}$ quipazine in rats pretreated with ritanserin or ICI 170,809 at the doses shown, or vehicle. $n = 6$ rats for each treatment group. * $P < 0.01$ compared with vehicle-treated controls.

general activity counts induced by a submaximally effective dose of apomorphine (0.3 mg kg$^{-1}$ s.c.): vehicle + apomorphine, median [inter quartile range] stereotypy score 14 [−1, +3], mean (± s.e.mean) activity counts 720 ± 62; ritanserin (0.4) + apomorphine, 13 [−2, +0], 770 ± 150; ritanserin (2) + apomorphine, 14.5 [−0.5, +0.5], 819 ± 84; ICI 170,809 (10) + apomorphine, 14 [−1, +1], 858 ± 158).

### *Effect of ritanserin and ICI 170,809 on quipazine-induced wet dog shake behaviour*

Both ritanserin and ICI 170,809 were tested for their ability to antagonize quipazine-induced wet dog shakes in rats, a model which has been used as an *in vivo* test of central 5-HT$_2$ receptor function. Ritanserin (0.05–1 mg kg$^{-1}$ s.c.) significantly and dose-dependently ($ID_{50}$ = 0.092 mg kg$^{-1}$) inhibited wet dog shake behaviour induced by quipazine administration (5 mg kg$^{-1}$ i.p.) (Figure 9a). Pretreatment with 1 mg kg$^{-1}$ ritanserin completely abolished the production of wet dog shake behaviour by quipazine.

ICI 170,809 (0.05–5 mg kg$^{-1}$ s.c.) also significantly and dose-dependently ($ID_{50}$ = 1.41 mg kg$^{-1}$) inhibited quipazine-induced wet dog shake behaviour (5 mg kg$^{-1}$ i.p.) (Figure 9b). Pretreatment with 5 mg kg$^{-1}$ ICI 170,809 completely abolished the production of wet dog shake behaviour by quipazine.

## Discussion

The results of the present study show that pretreatment with the 5-HT$_2$/5-HT$_{1C}$ antagonist ritanserin enhanced all components of the 5-HT behavioural syndrome when induced in rats by the 5-HT$_{1A}$ receptor agonists 8-OH-DPAT, 5-MeODMT and gepirone. A second 5-HT$_2$/5-HT$_{1C}$ antagonist, ICI 170,809, similarly increased the 5-HT behavioural syndrome when induced by either 8-OH-DPAT or 5-MeODMT. On their own neither ritanserin nor ICI 170,809 produced any component of the 5-HT behavioural syndrome. Furthermore, neither compound had any effect on stereotypy or locomotor activity induced by a submaximally effective dose of the dopamine agonist apomorphine. These latter findings suggest that ritanserin and ICI 170,809 do not enhance the 5-HT behavioural syndrome through non-specific activation. It is unlikely that these drugs act by inhibiting the metabolism of the 5-HT$_{1A}$ agonists, since those used have a markedly different chemical structure and most probably do not have a common metabolic pathway.

Both ritanserin and ICI 170,809 potently inhibited wet dog shake behaviour induced by quipazine in rats, a model which has previously been used as an *in vivo* test of 5-HT$_2$ receptor function (Vetulani *et al.*, 1980; Colpaert & Janssen, 1983; Yap & Taylor, 1983). In fact, the relationship between dose and effect for inhibiting wet dog shake behaviour and for enhancing the behavioural syndrome coincided well for each compound. For example, ritanserin almost completely abolished quipazine-induced wet dog shake behaviour at a dose (0.4 mg kg$^{-1}$) which produced maximal enhancement of 8-OH-DPAT-induced behaviour. However, in the light of the similarities between the pharmacology of the 5-HT$_2$ and 5-HT$_{1C}$ receptors (see Hoyer, 1988b), it cannot be certain that quipazine-induced wet dog shakes occur solely through activation of 5-HT$_2$ receptors.

In a low dose ketanserin, which also has 5-HT$_2$ antagonist activity (Leysen *et al.*, 1981), also potentiated the 5-HT behavioural syndrome, while a higher dose of the drug inhibited the response. Previously, higher doses of ketanserin have been shown to inhibit the 8-OH-DPAT and 5-MeODMT-induced behavioural syndrome (Tricklebank *et al.*, 1984; 1985). The blockade of the 5-HT behavioural syndrome by higher doses of ketanserin might arise from actions on other receptors or other neurotransmitters, in particular the $\alpha_1$-adrenoceptor for which ketanserin is a potent ligand (Leysen *et al.*, 1981). In the present study, we found that the $\alpha_1$-adrenoceptor antagonist prazosin markedly reduced the 5-HT behavioural syndrome induced by 8-OH-DPAT, confirming the findings of Tricklebank *et al.* (1984). Ketanserin also has actions on dopamine receptors and both this study and that of Tricklebank *et al.* observed blockade of the 8-OH-DPAT-induced syndrome by the dopamine antagonist haloperidol. Thus, enhancement of the 5-HT behavioural syndrome by a low dose of ketanserin could reflect the preferential 5-HT$_2$ antagonist action of the drug, whereas $\alpha_1$-adrenoceptor and/or dopamine antagonism might account for the high dose inhibition of the 8-OH-DPAT- and 5-MeODMT-induced behavioural syndrome. Antagonism of catecholamine receptors might also explain the results of earlier studies, which demonstrated that putative 5-HT$_2$ antagonists including spiperone and pirenperone decreased various components of the 5-HT behavioural syndrome (Ortmann *et al.*, 1982; Green *et al.*, 1983; Goodwin & Green, 1985). In one study, Goodwin & Green (1985) found that ritanserin had no effect on the 8-OH-DPAT-induced behavioural syndrome, although a maximally effective dose of 8-OH-DPAT (3 mg kg$^{-1}$ s.c.) was used (cf. Figure 5).

Both ritanserin and ICI 170,809 were recently shown to have an affinity for the central 5-HT$_{1C}$ binding site which was only slightly less than that for the 5-HT$_2$ binding site (Hoyer, 1988a; Blackburn personal communication). However, it has been found that ritanserin at doses larger than those used here is not active in a putative behavioural model of 5-HT$_{1C}$ function (Kennett & Curzon, 1988). In addition, ketanserin, shows at least a 70 fold greater affinity for 5-HT$_2$ versus 5-HT$_{1C}$ receptors (Hoyer, 1988a). These observations therefore favour 5-HT$_2$, rather than 5-HT$_{1C}$, sites as the mediator of the 5-HT$_{1A}$ enhancing effects of ritanserin, ICI 170,809 and ketanserin. However, the role of 5-HT$_{1C}$ receptors in this respect would be best clarified with the aid of selective 5-HT$_{1C}$ antagonists. Unfortunately such drugs are not currently available.

One explanation of our finding that ritanserin, ICI 170,809 and ketanserin increase the 5-HT$_{1A}$-mediated behavioural syndrome is that endogenous 5-HT exerts a tonic inhibitory effect on 5-HT$_{1A}$ receptor function via 5-HT$_2$ or possibly

5-$HT_{1C}$ receptors, and that blockade of these receptors releases 5-$HT_{1A}$ receptors from this inhibitory influence. There are several lines of evidence which support such an idea. (1) Ritanserin enhances the behavioural activation in rats induced by the 5-$HT_1$ agonist RU 24969 (Goodwin & Green, 1985; Backus *et al.*, unpublished finding). (2) Electrophysiological experiments show that ketanserin increases the inhibitory effects of iontophoretically applied 5-HT on neurones in rat prefrontal cortex (Lakoski & Aghajanian, 1985). Concurrent microiontophoretic application of another putative 5-$HT_2$ antagonist, TR2515, similarly enhances the depressant effect of 5-HT, lysergic acid diethylamide (LSD) and 8-OH-DPAT on dorsal raphe neurones (Blier *et al.*, 1989). (3) Biochemical experiments have shown that 5-HT acts on 5-$HT_{1A}$ receptors to suppress vasoactive intestinal peptide (VIP)-stimulated cyclic AMP production in cultured striatal and cortical neurones and, further, that this action of 5-HT is potentiated by ketanserin (Weiss *et al.*, 1986). (4) In man, ritanserin enhances the 5-$HT_1$ receptor-mediated increase of plasma prolactin and growth hormone induced by L-tryptophan (Charig *et al.*, 1986).

Recently, Arnt & Hyttel (1989) found that pretreatment with the putative 5-$HT_2$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (Shannon *et al.*, 1984) enhanced 8-OH-DPAT-induced forepaw treading in rats. Further, it was suggested that stimulation of 5-$HT_2$ receptors has a permissive role on the expression of the 5-$HT_{1A}$ function, which would appear to conflict with the conclusions of the present study. However, there is evidence that at least some aspects of the 5-HT behavioural syndrome can be induced by 5-$HT_2$ as well as 5-$HT_{1A}$ receptor activation. For example, we have observed that high doses of DOI induce a behavioural syndrome which is not unlike that of 8-OH-DPAT and which is sensitive to ritanserin (Wang *et al.*, unpublished observation). Furthermore, Goodwin & Green (1985) found that the behavioural syndrome induced by the 5-HT agonist quipazine is attenuated by both ritanserin and the 5-$HT_1$/$\beta$-adrenoceptor antagonist propranolol. In a model to account for the present findings and those of others, the 5-HT behavioural syndrome might be produced by stimulation of a population of either 5-$HT_{1A}$ or 5-$HT_2$ receptors, with the former being under the inhibitory influence of a sub-population of 5-$HT_2$ receptors.

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