Br. J. Pharmacol. (1988), **94**, 137–147

Evidence that mCPP may have behavioural effects mediated by central 5-HT_{1C} receptors

[1]G.A. Kennett & G. Curzon

Department of Neurochemistry, Institute of Neurology, Queen Square, London WC1N 3BG

1 The effects of 1-(3-chlorophenyl)piperazine (mCPP) and 1-[3-(trifluoromethyl)phenyl] piperazine (TFMPP) on activity of rats in a novel cage, and on the rotorod and elevated bar co-ordination tests was examined.

2 Peripherally administered mCPP and TFMPP dose-dependently reduced locomotion, rearing, and feeding scores but not grooming of freely fed rats placed in a novel observation cage. Yawning behaviour was increased. Similar effects were also observed after injection of mCPP into the 3rd ventricle.

3 Co-ordination on a rotating drum of both untrained and trained rats was impaired following mCPP but co-ordination on an elevated bar was not.

4 The hypoactivity induced by mCPP was opposed by three antagonists with high affinity for the 5-hydroxytryptamine (5-HT_{1C}) site; metergoline, mianserin, cyproheptadine and possibly also by a fourth antagonist mesulergine. Metergoline, mianserin and cyproheptadine also opposed the reduction in feeding scores. However, neither effect of mCPP was antagonized by the 5-HT_2-receptor antagonists ketanserin or ritanserin, the 5-HT_3-receptor antagonist ICS 205-930, the 5-HT_{1A} and 5-HT_{1B}-receptor antagonists (−)-pindolol, (−)-propranolol and (±)-cyanopindolol or the 5-HT_{1A}-, 5-HT_2- and dopamine receptor antagonist spiperone. The specific α_2-adrenoceptor antagonist idazoxan was also without effect.

5 Hypoactivity induced by TFMPP was similarly antagonized by mianserin but unaffected by (±)-cyanopindolol.

6 These results suggest that the hypoactivity is mediated by central 5-HT_{1C}-receptors and that mCPP and possibly TFMPP may be 5-HT_{1C}-receptor agonists.

7 As mianserin, cyproheptadine and mesulergine in the absence of mCPP did not increase locomotion but increased the number of feeding scores, the activation of 5-HT_{1C}-receptors may be of physiological importance in the control of appetite. The possible relevance of these results to the therapeutic and side-effects of clinically used antidepressants (particularly trazodone and mianserin) and anorexigenic drugs is discussed.

Introduction

Ligand binding studies have identified at least four (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C} and 5-HT_2; Peroutka & Snyder, 1979; Pedigo *et al.*, 1981; Pazos *et al.*, 1985; Blurton & Wood, 1986) and possibly five (5-HT_{1D}; Heuring & Peroutka, 1987) central 5-hydroxytryptamine (5-HT) receptor subtypes, and 5-HT_3-receptors have been identified in the periphery (Bradley *et al.*, 1986). Recently, we have observed that RU 24969, an agonist at 5-HT_{1B}- and to a lesser extent at 5-HT_{1A}-receptors (Hamon *et al.*, 1986; Tricklebank *et al.*, 1986) caused prolonged anorexia in freely fed rats by an action at postsynaptic 5-HT_{1B} sites (Kennett *et al.*, 1987).

Two other putative 5-HT_{1B}-receptor agonists, 1-(3-chlorophenyl)piperazine (mCPP) and 1-[3-(trifluoromethyl)phenyl]piperazine (TFMPP) (Sills *et al.*, 1984; Asarch *et al.*, 1985; Hamon *et al.*, 1986), are also anorexigenic (Samanin *et al.*, 1979; Kennett *et al.*, 1987). However, there are clear differences in the behaviour evoked by RU 24969 and these drugs, since at anorexigenic doses RU 24969 also causes hyperlocomotion (Green *et al.*, 1984; Tricklebank *et al.*, 1986) whilst TFMPP causes hypolocomotion (Lucki & Frazer, 1982). As RU 24969-induced hyper-

[1] Author for correspondence.

locomotion but not anorexia (Green *et al.*, 1984; Tricklebank *et al.*, 1986; Kennett *et al.*, 1987) is antagonized by haloperidol it is unlikely that the latter behaviour is due to the former. Furthermore, metergoline potentiates the hyperlocomotor response to RU 24969 (Green *et al.*, 1984; Tricklebank *et al.*, 1986) but antagonizes the anorexic response (Kennett *et al.*, 1987).

However, the anorexic effect of mCPP and TFMPP could conceivably be due to hypoactivity. In the present study, the effects of mCPP and TFMPP on locomotion and feeding bouts were studied following pretreatment with various 5-HT antagonists. The results suggest that both the hypoactivity and anorexia caused by mCPP and TFMPP in the present paradigm, involve agonistic effects at central 5-HT_{1C}-receptors.

Some of these data were presented as a communication to the British Pharmacological Society Meeting, September 1987 (Kennett & Curzon, 1987).

Methods

Behavioural testing procedure

Male Sprague-Dawley rats (200–250 g) were singly housed in standard cages with free access to food (Special Diet Services Ltd., Essex, England, RM1(E) rodent diet) and water under a 12 h light/dark cycle (lights on 06 h 00 min). Experiments were carried out in the same room between 10 h 00 min and 17 h 30 min. Rats were injected using a balanced design in pairs at 20 min intervals, firstly with vehicle or drug and 20 min later with mCPP, TFMPP or saline. Twenty min after the second injection they were each placed for the first time in a wire mesh observation cage 26 cm × 26 cm × 26 cm with sawdust covered floor. The cage contained five of their normal food pellets. Total numbers of cage crossings, rears, grooms, wet dog shakes, and yawns were recorded over the following 20 min by an observer with a hand held counter. Feeding scores were made by giving a point for each feeding bout and an extra point for every additional 20 s continuous feeding. Hindlimb abduction scores were rated on a 0–4 scale of intensity from 0 (absent) to 4 (maximal).

The effect of ketanserin on 5-hydroxytryptophan (5-HTP) and carbidopa-induced wet dog shakes was scored as follows. Rats were injected with carbidopa and either saline or ketanserin and placed in wire mesh observation cages. Thirty min later they were injected with 5-HTP and the number of head twitches counted for 2 min periods at 30, 60 and 90 min after injection. The scores were then summed.

The ability of rats to maintain their balance on a rotating drum (width 10 cm, diameter 13 cm with walls 17 cm high), rotating at 10 r.p.m. was recorded as an index of locomotor co-ordination with no pre-exposure. Rats were also tested after training so that they could maintain their balance on the apparatus for at least 20 s on the morning of the test. This was done to differentiate defects of co-ordination and of learning. The test was conducted under white light between 15 h 00 min and 17 h 00 min. Saline and mCPP treated animals were tested alternately 20 min after injection.

Another test of locomotor co-ordination was also used in which rats were trained (between 10 h 00 min and 12 h 00 min) to maintain their balance for 20 s on a horizontal plastic bar 2.2 cm wide, 91 cm long and clamped 35 cm from the ground. They were replaced on the bar 20 min after injection of saline or mCPP between 15 h 00 min and 17 h 00 min on the same day. The number of forepaw and hindpaw movements and the number of grooms were counted over 4 min using a hand held counter.

Surgical procedure

Rats were anaesthetized with sodium pentobarbitone (Sagatal, May and Baker Ltd., Dagenham, U.K.) (60 mg kg^{-1} i.p.) and placed in a Kopf model 900 stereotaxic frame. Following exposure of the skull surface a hole was drilled into the skull approximately 3 mm lateral to the bregma and a stainless steel attachment screw fitted. A further hole was drilled 1.3 mm caudal to the bregma through which a 23 gauge stainless steel guide cannula was implanted into the third ventricle (co-ordinates from bregma; Rostral caudal 1.3 mm, dorsoventral 4.5 mm, medial lateral 0 mm, Atlas; Paxinos & Watson, 1982). Guide cannulae were fixed in place using dental acrylic and the incision closed with surgical sutures. Guide cannulae lumens were prevented from blocking by the insertion of 30 gauge wire cut to length before surgery. Rats were left to recover for at least 72 h before experimentation.

On each of three experimental days rats were allocated to one of three different treatment groups (saline, 5 μg and 20 μg mCPP) by Latin square to avoid order effects. They were then injected (1 μl over 2 min) using a 30 gauge needle, slightly longer than the guide cannula, and a 10 μl Hamilton syringe. Two minutes after the end of injection the needle was removed from the guide cannula, the 30 gauge wire replaced and the rat placed in a novel cage for 20 min as previously. Placement of guide cannulae was checked by *post-mortem* sectioning following injection of a small quantity of dye.

Drugs

1-(3-Chlorophenyl)piperazine (mCPP) (Research Biochemical Inc., Wayland, M.A., U.S.A.), 1-[3-(trifluoromethyl)phenyl]piperazine hydrochloride

(TFMPP) (Research Biochemicals Inc.), idazoxan (Reckitt and Colman Pharmaceutical Division, Kingston Upon Hull, U.K.), and ICS 205-930 ((3α-tropanyl)-1H-indole-3-carboxylic acid ester) (Sandoz Ltd., Basel, Switzerland) were dissolved in 0.9% NaCl and injected either i.p. (mCPP and TFMPP) or s.c. at the back of the neck (idazoxan and ICS 205-930). (−)-Propanolol (I.C.I., Macclesfield, U.K.) was also dissolved in saline and neutralised to pH 6.5 with NaOH before s.c. injection. Metergoline (Farmitalia), (−)-pindolol, (±)-cyanopindolol and mesulergine (all Sandoz Ltd., Basel), spiperone, ritanserin and ketanserin (all Janssen, Beerse, Belgium), cyproheptadine (Merck, Sharp and Dohme Research Laboratories, Harlow, Essex, U.K.) and mianserin (Organon Laboratories Ltd., Newhouse, U.K.) were all dissolved in 100–200 μl of 10% acetic acid, made up to almost the required volume with 0.9% NaCl and neutralised to pH 6.5. The required volume was then made up with saline and injected subcutaneously. Carbidopa (Merck Sharp and Dohme Research Laboratories) and 5-HTP (Sigma Chemical Company Ltd., Poole, Dorset, U.K.) were given as suspensions in 0.9% NaCl with 0.005% BRIJ 35 (Polyoxyethylene lauryl ether). All drugs were given in volumes of 1 ml kg^{-1} rat body weight except for carbidopa and 5-HTP which were given in volumes of 4 ml kg^{-1} body weight.

Statistical methods

Rotorod or elevated bar test results were analysed by 2 tailed Student's *t* test. Other data were tested for significance by use of Dunnett's multiple comparisons procedure following a significant one way analysis of variance test (ANOVA).

Results

Effects of mCPP and TFMPP on activity

Table 1 shows that both mCPP and TFMPP dose-dependently reduced the number of cage crossings, rears and feeding scores. A significant increase in yawning was also observed after administration of 10 mg kg^{-1} mCPP or TFMPP. However, there was no significant change in the number of grooms or in the small number of 'wet dog' shakes (data not shown) following mCPP and TFMPP, respectively. The only other behaviour observed was a small but not significant degree of limb abduction at the highest doses used. (mCPP 10 mg kg^{-1}: limb abduction 0.8 ± 0.3 (mean ± s.e. mean), NS. TFMPP: 10 mg kg^{-1}, limb abduction 0 ± 0, NS). Table 2 shows that mCPP potently impaired the ability of both untrained and trained rats to maintain their balance on a rotating drum but did not affect their behaviour on a stationary elevated bar, when numbers of forepaw movements, hindpaw movements and grooms were unaltered and all rats maintained their balance over the 4 min test period.

Inhibition of mCPP-induced hypoactivity by the non-specific 5-HT-receptor antagonist metergoline

The non-specific 5-HT-receptor antagonist metergoline (5 mg kg^{-1} s.c.) did not affect the numbers of cage crossings, rears or feeding scores of saline-treated rats but blocked their reduction following mCPP (5 mg kg^{-1} i.p.; Table 3).

Lack of effect of the 5-HT$_2$-receptor antagonists ketanserin and ritanserin and the 5-HT$_3$-receptor antagonist ICS 205-930 on mCPP-induced hypoactivity: effect of ketanserin on 5-HTP and carbidopa-induced 'wet dog' shakes

The specific 5-HT$_2$ antagonists ketanserin (0.2 mg kg^{-1}) was without effect on the activity of saline or mCPP treated rats (Table 4). This dose of ketanserin markedly inhibited carbidopa (25 mg kg^{-1}, i.p.) + 5-HTP (100 mg kg^{-1} i.p.)-induced 'wet dog' shakes, a behaviour thought to be mediated by 5-HT$_2$-receptor activation: saline pretreated: 20.9 ± 5.2 shakes, ketanserin pretreated 2.0 ± 0.63 shakes (mean ± s.d., $n = 6$ per group, $P < 0.005$, by two tailed Student's *t* test). Another specific 5HT$_2$-receptor antagonist ritanserin (0.63 mg kg^{-1}) and the specific 5-HT$_3$-receptor antagonist ICS 205-930 also had no effect on the activity of saline or mCPP-treated rats (Table 4).

Lack of effect of various drugs with antagonist properties at 5-HT$_{1A}$, 5-HT$_{1B}$ and other receptors on mCPP-induced hypoactivity

Spiperone (0.05 mg kg^{-1}) a 5-HT$_{1A}$-, 5-HT$_2$- and dopamine-receptor antagonist decreased cage crossings of saline-treated rats, but did not reduce their feeding scores and did not affect mCPP-induced hypoactivity or anorexia. (−)-Pindolol (2 mg kg^{-1}) and (±)-cyanopindolol (8 mg kg^{-1}) and (−)-propranolol (16 mg kg^{-1}) which antagonize both 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors did not affect the activity of saline-treated rats and (like spiperone) did not alter mCPP-induced hypoactivity or reduction in feeding scores (Table 5).

Inhibition of mCPP-induced hypoactivity by drugs with high affinity for 5-HT$_{1C}$-receptors

Pretreatment of rats with mianserin (2 mg kg^{-1}) significantly increased the feeding scores of saline-

Table 1 The effects of i.p. administration of mCPP and TFMPP on the activity of rats placed for 20 min in a novel observation cage 20 min later

Treatment		*Cage crossing*	*Rears*	*Grooms*	*Feeding bouts*	(n)
Saline		62 ± 4	53 ± 3	4.9 ± 0.7	6.5 ± 1.1	(8)
mCPP	1 mg kg^{-1}	46 ± 8	41 ± 5	9.0 ± 2.0	3.2 ± 1.4*	(8)
	2 mg kg^{-1}	25 ± 6**	32 ± 5**	9.1 ± 2.6	0.9 ± 0.5**	(8)
	5 mg kg^{-1}	6 ± 1**	4 ± 2**	3.1 ± 0.7	0 ± 0**	(8)
	10 mg kg^{-1}	3 ± 1**	2 ± 1**	4.3 ± 2.1	0 ± 0**	(8)
Saline		60 ± 7	43 ± 4	6.6 ± 1.2	10.3 ± 2.8	(7)
TFMPP	2 mg kg^{-1}	38 ± 5**	29 ± 4*	5.6 ± 2.3	6.3 ± 1.7	(7)
	5 mg kg^{-1}	12 ± 3**	6 ± 2**	5.6 ± 2.3	0.1 ± 0.1**	(7)
	10 mg kg^{-1}	5 ± 2**	1 ± 1**	3.2 ± 1.5	0 ± 0**	(5)

Results shown are means ± s.e. mean. Significantly different from saline-treated group $*P < 0.05$, $**P < 0.01$ by Dunnett's test following a significant ANOVA.

Table 2 The effects of i.p. mCPP on rotorod and elevated bar performance 20 min later

	Time on rotorod (s)		
Treatment	*Untrained*	*Trained*	
Saline	22.2 ± 8.8	22.3 ± 4.6	
mCPP 2 mg kg^{-1}	6.6 ± 3.2	4.6 ± 0.4**	
5 mg kg^{-1}	3.35 ± 0.4*		
	Behaviour on bar (no. of movements/4 min)		
	Forepaw	*Hindpaw*	*Grooms*
Saline	29.4 ± 7.2	17.1 ± 5.8	3.1 ± 1.2
mCPP 2 mg kg^{-1}	26.0 ± 6.0	15.2 ± 3.1	1.0 ± 1.1

Results shown are means ± s.e. mean, $n = 7$ per group. Significantly different from saline-treated group $*P < 0.05$, $**P < 0.01$ by 2 tailed Student's t test.

Table 3 Inhibition of mCPP (5 mg kg^{-1} i.p.)-induced hypoactivity by the non-specific 5-HT-receptor antagonist metergoline (5 mg kg^{-1} s.c.) given 20 min earlier

Treatment (n)	*Cage crossings*	*Rears*	*Feeding bouts*
Vehicle + saline (8)	62 ± 4	53 ± 3	6.5 ± 1.1
Metergoline + saline (8)	58 ± 5	44 ± 5	6.7 ± 0.9
Vehicle + mCPP (8)	6 ± 1**	4 ± 2**	0 ± 0
Metergoline + mCPP (8)	45 ± 2††	40 ± 4††	4.9 ± 1.7†

Results shown are means ± s.e. mean. Activity on placement in an observation cage for 20 min was scored 20 min after mCPP injection. Significantly different from vehicle + saline-treated group, $*P < 0.05$, $**P < 0.01$; or from vehicle + mCPP-treated group † $P < 0.05$, †† $P < 0.01$ by Dunnett's test following significant ANOVA.

treated rats but did not alter cage crossing or rearing. It opposed the actions of mCPP on cage crossing, rearing and feeding scores although the number of rears in the mianserin + mCPP group was still somewhat less than in the vehicle + saline group and the feeding scores less than that shown by rats treated with mianserin + saline (Table 6). Cyproheptadine and mesulergine had similar effects to those of mianserin. Thus, cyproheptadine alone (2 mg kg^{-1}) increased the number of feeding scores of saline-treated rats but did not alter other behaviours, except for grooming (vehicle + saline 5.8 ± 1.1, cyproheptadine + saline 1.3 ± 0.5, mean ± s.e. mean, $n = 6$ per group, $P < 0.05$ by Dunnett's test following ANOVA) and body shakes (vehicle + saline 4.2 ± 0.7, cyproheptadine + saline 0.5 ± 0.3,

Table 4 Failure of pretreatment (s.c.) with the 5-HT$_2$-receptor antagonists ketanserin (0.2 mg kg^{-1}) and ritanserin (0.63 mg kg^{-1}) or the 5-HT$_3$-receptor antagonist ICS 205-930 (1 mg kg^{-1}) to reverse hypoactivity induced by mCPP (5 mg kg^{-1} i.p.) given 20 min later

Treatment (n)	*Cage crossings*	*Rears*	*Feeding bouts*
Vehicle + saline (8)	53 ± 5	48 ± 5	5.9 ± 1.1
Ketanserin + saline (7)	49 ± 5	44 ± 4	8.3 ± 1.0
Vehicle + mCPP (8)	7 ± 1**	4 ± 1*	0 ± 0*
Ketanserin + mCPP (7)	6 ± 1††	4 ± 2††	0 ± 0††
Vehicle + saline (6)	58 ± 6	41 ± 4	6.3 ± 1.2
Ritanserin + saline (6)	53 ± 5	38 ± 6	7.4 ± 1.0
Vehicle + mCPP (5)	6 ± 2**	4 ± 2**	0 ± 0*
Ritanserin + mCPP (5)	9 ± 4††	6 ± 4††	0 ± 0†
Vehicle + saline (6)	57 ± 5	36 ± 1	3.2 ± 0.9
ICS 205-930 + saline (5)	43 ± 6	30 ± 4	8.4 ± 4.3
Vehicle + mCPP (6)	9 ± 3**	8 ± 3**	0 ± 0
ICS 205-930 + mCPP (5)	10 ± 2††	2 ± 1††	0 ± 0†

Results shown are means ± s.e. mean. Activity on placement in an observation cage for 20 min was scored 20 min after mCPP injection. Significantly different from vehicle-treated controls *$P < 0.05$, **$P < 0.01$, from drug-treated controls †$P < 0.05$, ††$P < 0.01$ by Dunnett's test following significant ANOVA.

Table 5 Failure of s.c. pretreatment with drugs with 5HT$_{1A}$ or 5HT$_{1B}$ antagonist activity to reverse hypoactivity induced by mCPP (5 mg kg^{-1} I.P.) given 20 min later

Treatment (n)	*Cage crossings*	*Rears*	*Feeding bouts*
Vehicle + saline (8)	53 ± 6	42 ± 5	11.3 ± 4
(−)-Pindolol + saline (7)	58 ± 7	34 ± 6	9.0 ± 1.1
Spiperone + saline (7)	31 ± 2**	23 ± 2**	14.2 ± 2.3
Vehicle + mCPP (8)	14 ± 2**	9 ± 2**	1.8 ± 3.0*
(−)-Pindolol + mCPP (7)	12 ± 4††	8 ± 3†	0.9 ± 0.9†
Spiperone + mCPP (8)	1 ± 1††	1 ± 1†	0 ± 0††
Vehicle + saline (8)	62 ± 4	41 ± 2	4.2 ± 1.0
(±)-Cyanopindolol + saline (5)	75 ± 8	51 ± 2	8.0 ± 4.0
Vehicle + mCPP (6)	19 ± 4**	14 ± 3**	0.5 ± 0.3
(±)-Cyanopindolol + mCPP (5)	14 ± 4††	11 ± 4†	0.6 ± 0.4
Vehicle + saline (5)	60 ± 4	36 ± 5	2.3 ± 1
(−)-Propranolol + saline (4)	64 ± 9	37 ± 7	0.2 ± 0.2
Vehicle + mCPP (4)	6 ± 2**	9 ± 4	0 ± 0
(−)-Propranolol + mCPP (4)	3 ± 1††	2 ± 1††	0 ± 0

Results shown are means ± s.e. mean.
Activity on placement in an observation cage for 20 min was scored 20 min after mCPP injection. Significantly different from controls *$P < 0.05$, **$P < 0.01$, from drug-treated controls †$P < 0.05$, ††$P < 0.01$. The doses of the drugs used were: (−)-pindolol (2 mg kg^{-1}), spiperone (0.05 mg kg^{-1}), (±)-cyanopindolol (8 mg kg^{-1}) and (−)-propranolol (16 mg kg^{-1}).

$P < 0.05$) which were reduced. Cyproheptadine also opposed the reduction of cage crossing, rearing and feeding scores by mCPP. Antagonism of the inhibition of feeding was complete, but antagonism of the reduction in cage crossing and rearing was partial (Table 6). Mesulergine 0.1 mg kg^{-1} and 0.2 mg kg^{-1} increased the feeding scores of saline-treated rats but reduced locomotion and rearing. The drug also inhibited grooming (vehicle + saline 6.7 ± 1.0, mesulergine 0.2 mg kg^{-1} + saline 1.7 ± 0.8, $n = 6$–7, $P < 0.05$). However, despite these indications of sedation, some antagonism of the effects of mCPP were suggested in that, with the higher dose of mesulergine, scores for locomotion or rearing of mesulergine + saline and mesulergine + mCPP groups were not significantly different. This dose, however, did not reverse the anorexic effect of mCPP.

Table 6 Effects of drugs with high affinity for 5-HT_{1C} receptors: mianserin ($2\,mg\,kg^{-1}$), cyproheptadine ($2\,mg\,kg^{-1}$) and mesulergine (0.1 or $0.2\,mg\,kg^{-1}$) on hypoactivity induced by mCPP ($5\,mg\,kg^{-1}$ i.p.) given 20 min later

Treatment (n)	*Cage crossings*	*Rears*	*Feeding bouts*
Vehicle + saline (8)	53 ± 5	48 ± 5	5.9 ± 1.1
Mianserin + saline (7)	61 ± 2	38 ± 3	12.8 ± 5**
Vehicle + mCPP (8)	7 ± 1**	4 ± 1*	0 ± 0*
Mianserin + mCPP (7)	52 ± 5§	27 ± 6§	7.1 ± 2.4§
Vehicle + saline (6)	73 ± 2	56 ± 4	7.2 ± 1.1
Cyproheptadine + saline (6)	68 ± 8	51 ± 4	16.3 ± 1.8*
Vehicle + mCPP (6)	16 ± 5**	14 ± 3**	0.2 ± 0.2*
Cyproheptadine + mCPP (6)	48 ± 8§	23 ± 5††	15.5 ± 4.6†§
Vehicle + saline (6)	57 ± 6	36 ± 1	3.2 ± 0.9
Mesulergine (0.1) + saline (3)	48 ± 7	30 ± 1	10 ± 0.6**
Mesulergine (0.2) + saline (6)	29 ± 2**	25 ± 4	10 ± 2**
Vehicle + mCPP (6)	9 ± 3	8 ± 3	0 ± 0
Mesulergine (0.1) + mCPP (5)	19 ± 5†	13 ± 6††	0.7 ± 0.7††
Mesulergine (0.2) + mCPP (6)	18 ± 4	16 ± 5	1.6 ± 1.5††

Results shown are means ± s.e. mean.
Activity on placement in an observation cage for 20 min scored 20 min after mCPP injection. Significantly different from control *$P < 0.05$, **$P < 0.01$, from drug-treated control †$P < 0.05$, ††$P < 0.01$, or from mCPP-treated group §$P < 0.01$ by Dunnett's test following significant ANOVA.

Lack of effect of idazoxan on mCPP-induced hypoactivity

The α_2-adrenoceptor antagonist idazoxan ($1\,mg\,kg^{-1}$) alone had no significant effects on the behaviour of saline-treated rats (Table 7) and did not significantly oppose mCPP-induced behaviour.

Effects of cyanopindolol and mianserin on TFMPP-induced hypoactivity

Results obtained with TFMPP (Table 8) paralleled those previously found for mCPP in that the locomotor and rearing deficits were unaffected by cyanopindolol ($8\,mg\,kg^{-1}$) but reversed by mianserin ($2\,mg\,kg^{-1}$). However, in this experiment, mianserin did not significantly increase feeding scores in saline-treated rats and did not reverse the reduction in feeding scores following TFMPP.

Lack of effect of mianserin and cyproheptadine on activity in the absence of food

Previous results showed that mianserin, cyproheptadine and mesulergine all increased feeding scores, but not locomotor activity or rearing in a novel cage. It seemed possible that locomotor activity might have been enhanced but for the presence of food and faecal pellets. However, at no dose tested did either mianserin or cyproheptadine affect activity in a novel cage in the absence of food (Table 9).

Table 7 Failure of s.c. pretreatment with the α_2-adrenoceptor antagonist idazoxan ($1\,mg\,kg^{-1}$) to reverse hypoactivity induced by mCPP ($5\,mg\,kg^{-1}$ i.p.) given 20 min later

Treatment (n)	*Cage crossings*	*Rears*	*Feeding bouts*
Vehicle + saline (6)	73 ± 2	56 ± 4	7.2 ± 1.1
Idazoxan + saline (5)	86 ± 8	57 ± 8	7.6 ± 1.2
Vehicle + mCPP (6)	16 ± 5**	14 ± 3**	0.2 ± 0.2*
Idazoxan + mCPP (5)	26 ± 7††	21 ± 5††	0.6 ± 0.6†

Results shown are means ± s.e. mean.
Activity on placement in an observation cage for 20 min was scored 20 min after mCPP injection. Significantly different from vehicle-treated control *$P < 0.05$, **$P < 0.01$, from idazoxan-treated control †$P < 0.05$, ††$P < 0.01$ by Dunnett's test following significant ANOVA.

Table 8 Effect of (±)-cyanopindolol (8 mg kg^{-1}) and mianserin (2 mg kg^{-1}) given (s.c.) 20 min earlier on TFMPP (5 mg kg^{-1} i.p.)-induced hypoactivity

Treatment (n)	*Cage crossings*	*Rears*	*Feeding bouts*
Vehicle + saline (7)	60 ± 7	43 ± 4	10.3 ± 2.8
Cyanopindolol + saline (5)	65 ± 5	50 ± 3	8.2 ± 2.0
Mianserin + saline (5)	70 ± 8	43 ± 3	16.2 ± 1.8
Vehicle + TFMPP (7)	12 ± 3**	6 ± 2**	0.1 ± 0.1**
Cyanopindolol + TFMPP (5)	15 ± 4††	8 ± 3††	0.6 ± 0.4†
Mianserin + TFMPP (5)	50 ± 5§§	21 ± 4§††	0.8 ± 0.3†

Results shown are means ± s.e. mean.
Activity on placement in an observation cage for 20 min was scored 20 min after TFMPP injection. Significantly different from control *$P < 0.05$, **$P < 0.01$, from drug-treated group †$P < 0.05$, ††$P < 0.01$, or from mCPP-treated group §$P < 0.05$, §§$P < 0.01$ by Dunnett's test following significant ANOVA.

Table 9 Effect of mianserin and cyproheptadine injection (s.c.) 40 min earlier, on activity in an observation cage free of food or faecal pellets for 20 min

Treatment (n)	*Cage crossings*	*Rears*
Saline (17)	44.2 ± 4.1	46.2 ± 3.1
Mianserin 1 mg kg^{-1} (7)	31.5 ± 4.1	43.0 ± 4.7
2 mg kg^{-1} (14)	56.1 ± 6.4	42.1 ± 3.9
4 mg kg^{-1} (7)	38.3 ± 3.9	45.0 ± 5.7
Cyproheptadine 2 mg kg^{-1} (5)	53.9 ± 6.3	36.4 ± 4.8

Results shown are means ± s.e. mean.
No significant differences were found.

Effect of central injections of mCPP into the 3rd ventricle

Injections of mCPP into the third ventricle reproduced the effects of peripheral administration significantly reducing activity and reducing feeding scores (albeit not significantly in this paradigm). However, no sign of limb abduction was observed at the doses used (Table 10).

Discussion

mCPP and TFMPP dose-dependently reduced locomotion and rearing but not grooming, as previously demonstrated for TFMPP (Lucki & Frazer, 1982). Feeding behaviour was also reduced as shown for mCPP by Samanin *et al.* (1979) in food-deprived, and by Kennett *et al.* (1987) in freely-fed rats. We first examined the possibility that the effects of the drugs depended on gross locomotor impairment using a rotorod test as a measure of co-ordination. mCPP-treated rats showed impairment which did not appear to be due to inability to learn the task as pretrained rats were also impaired. However, no evidence of a co-ordination impairment was found in a second test in which forelimb and hindlimb movements on an elevated bar were scored separately. The absence of a hindlimb impairment in this latter

Table 10 Effect of an injection of mCPP (1 µl over 2 min) into the third ventricle on activity when placed in an observation cage for 20 min 2 min later

Treatment (n)	*Squares crossed*	*Rears*	*Grooms*	*Feeding scores*
Saline (8)	63.9 ± 5.3	43.8 ± 4.5	9.2 ± 1.6	4.2 ± 1.7
mCPP 5 µg (7)	47.1 ± 4.4*	34.3 ± 7.1	8.4 ± 2.7	1.1 ± 0.7
mCPP 20 µg (7)	21.8 ± 3.2**	22.9 ± 5.0*	11.1 ± 2.1	0.7 ± 0.7

Results shown are means ± s.e. mean.
Significantly different from saline-treated group *$P < 0.05$, **$P < 0.01$ by Dunnett's test following significant ANOVA.

test argues against mediation of hypoactivity by the hindlimb abduction observed to a slight degree in the present and previous studies (Samanin *et al.*, 1979; Ortmann, 1984) at the highest dose used. The rotorod data may therefore best be explained by a sedative action of mCPP, as suggested by yawning behaviour at the highest dose. This is consistent with data that mCPP causes sedation in monkeys as indicated by eye closure (Aloi *et al.*, 1984). The effects of mCPP on locomotion and feeding might also be caused by its clinically observed anxiogenic effect (Charney *et al.*, 1987), although this could be a non-specific response to the perceived effects of the drug.

The antagonism of the actions of mCPP on locomotion and feeding by metergoline, a non-specific 5-HT-receptor antagonist (Leysen *et al.*, 1981; Engel *et al.*, 1986), suggests mediation by 5-HT receptors. However the failure of the 5-HT_{1A}- and 5-HT_{1B}-receptor antagonists (−)-pindolol, (−)-propranolol and (±)-cyanopindolol (Hoyer *et al.*, 1985; Engel *et al.*, 1986) and of the 5-HT_{1A}-receptor antagonist spiperone to antagonize the effects of mCPP at doses which block the above receptor subtypes (Tricklebank *et al.*, 1984; Kennett *et al.*, 1987) indicates that neither is involved. As spiperone is a potent dopamine- and 5-HT_2-receptor antagonist (Leysen *et al.*, 1981) whilst (−)-pindolol, (−)-propranolol and cyanopindolol are potent β-receptor antagonists (Engel *et al.*, 1981) the results suggest that these receptors are also not involved. Indeed mCPP has a very low affinity for dopamine receptors (Invernizzi *et al.*, 1981).

The failure of the specific 5-HT_2-receptor antagonists ketanserin (Leysen *et al.*, 1981) and ritanserin (Leysen *et al.*, 1985) to oppose the effects of mCPP, and the report by Lucki & Frazer, (1982) that another 5-HT_2-receptor antagonist pipamperone did not oppose TFMPP-induced hypoactivity argue strongly against the involvement of 5-HT_2 receptors. The dose of ketanserin used almost abolished head twitches induced by carbidopa + 5-hydroxytryptophan, a behaviour mediated by 5-HT_2 receptors (Bedard & Pycock, 1977). The dose of ritanserin used also blocks 5-HT_2 receptors *in vivo* (Leysen *et al.*, 1985). Furthermore, mediation of the effects of mCPP by 5-HT_3 receptors seems unlikely since ICS 205-930 a potent 5-HT_3-receptor antagonist (Richardson *et al.*, 1985) was inactive at a probably relevant dose (Shearman & Tolcsvai, 1987).

The inhibition of locomotion and feeding by mCPP and TFMPP thus appears to be mediated by 5-HT receptors which are not of the 5-HT_{1A}, 5-HT_{1B}, 5-HT_2 or 5-HT_3 type. Since mCPP has low affinity for 5HT_{1D} receptors (Heuring & Peroutka, 1987) this subtype too is probably excluded. Therefore the inhibition by metergoline may depend on its high affinity for 5-HT_{1C} receptors (Hoyer *et al.*, 1985). This seems likely as two other 5-HT antagonists with high affinity for 5-HT_{1C}- but not 5-HT_{1D}- (Heuring & Peroutka, 1987) or 5-HT_{1B}-receptors, mianserin and cyproheptadine (Hoyer *et al.*, 1985; Engel *et al.*, 1986; Blurton & Wood, 1986) opposed the effects of mCPP. A third putative 5-HT_{1C} antagonist mesulergine (Hoyer *et al.*, 1985) also tended to oppose mCPP-induced hypoactivity but this effect was unclear since the drug itself decreased activity perhaps via activation of dopamine receptors (Closse, 1983). Although cyproheptadine and mianserin also have high affinity for histamine H_1-sites (Leysen *et al.*, 1981) this explains neither the effects of metergoline which does not have high affinity for these sites (Leysen *et al.*, 1981), nor the (less clear) effect of mesulergine (Closse, 1983). Furthermore, H_1-receptor antagonists themselves are sedative (Snyder, 1980).

Another possibility is that the behavioural effects of mCPP under consideration are mediated by its affinity for α_2-adrenoceptors (Smith & Suckow, 1985) as α_2-adrenoceptor agonists such as clonidine cause sedation (Clineschmidt *et al.*, 1979). However, the specific α_2-adrenoceptor antagonist idazoxan (Scatton *et al.*, 1983) at a relevant dose (Dickinson *et al.*, 1987) affected neither the hypoactivity nor the anorexia due to mCPP. Furthermore, even though mianserin, but not cyproheptadine, metergoline (Leysen *et al.*, 1981) or mesulergine (Closse, 1983) has appreciable affinity for α_2-receptors, it blocks the effects of mCPP at less than 1/10th of the dose needed to oppose clonidine-induced hypoactivity (Clineschmidt *et al.*, 1979; Nickolson *et al.*, 1982). Also, binding data suggest that the affinity of mianserin for α_2-receptors is much less than that for 5-HT_{1C}-receptors (Leysen *et al.*, 1981; Hoyer *et al.*, 1985; Blurton & Wood, 1986). The affinity of mCPP for α_1-receptors (Invernizzi *et al.*, 1981) also seems unlikely to mediate its hypoactive effects since α_1-adrenoceptor agonists cause hyperactivity (Clineschmidt *et al.*, 1979).

The above evidence, and the effect of central infusion of mCPP suggests that it alters activity and feeding by activating central 5HT_{1C}-receptors. These receptors are widely distributed in rat brain regions including the hypothalamus (Pazos & Palacios, 1985; Blurton & Wood, 1986). Results obtained with TFMPP are consistent with a similar mechanism since its effects on activity were sensitive to mianserin but not to (±)-cyanopindolol. Previously, the behavioural actions of mCPP and TFMPP were ascribed exclusively to their affinities for the 5-HT_{1B} and 5-HT_{1A} sites (Sills *et al.*, 1984; Asarch *et al.*, 1985; Kennett *et al.*, 1987), mainly because only two types of high affinity [^{3}H]-5-HT binding sites were recognised, the 5-HT_{1A} and the 5-HT_{1B} subtypes

(Pedigo *et al.*, 1981; Middlemiss & Fozard, 1983). As the latter group also includes 5-HT$_{1C}$- and perhaps also 5HT$_{1D}$-receptors (Pazos *et al.*, 1985; Heuring & Peroutka, 1987), the effects of 5-HT$_1$-receptor agonists and antagonists require re-evaluation.

As RU 24969 caused anorexia by an agonist action at 5-HT$_{1B}$ receptors the anorexic effects of mCPP and TFMPP were previously also ascribed to their known 5-HT$_{1B}$-receptor agonist properties (Kennett *et al.*, 1987). However, in the present study, 5-HT$_{1C}$-receptor antagonists (apart from mesulergine) but not 5-HT$_{1B}$-receptor antagonists opposed the mCPP-induced reduction in feeding bouts. Conversely, antagonists with high affinity for 5-HT$_{1C}$ receptors (apart from metergoline) increased feeding scores while antagonists at 5-HT$_{1B}$-, 5-HT$_{1A}$-, 5-HT$_2$-, 5-HT$_3$- or dopamine receptors, or α_2-adrenoceptors did not, in both the present study and previously (Kennett *et al.*, 1987). Therefore, activation of 5-HT$_{1C}$ receptors may be involved in the anorexic effect of drugs which increase synaptic concentrations of 5-HT e.g. fenfluramine, fluoxetine and zimelidine (Blundell, 1984; Pinder *et al.*, 1975) and their blockade may mediate the enhanced appetite and weight gain of patients treated with mianserin or cyproheptadine (Hopman, 1980; Pinder *et al.*, 1980; Bergen, 1964). It is also possible that the sedative side-effects of Trazodone (Feighner, 1980; Goldberg & Finnerty, 1980) involve its known metabolism to mCPP (Caccia *et al.*, 1982).

The apparent anorexic effects of mCPP and TFMPP could be secondary to hypolocomotion, although there is some suggestion that the former is more sensitive to mCPP than the latter. However, the ability of cyproheptadine, mianserin and mesulergine to increase feeding scores but not locomotion suggests that the two effects are dissociated. Indeed mesulergine alone had a strong hypolocomotor effect. However, the hypophagic and hyperphagic responses to 5-HT$_{1C}$-receptor agonists and antagonists, respectively could conceivably involve separate mechanisms.

Our main conclusions are that mCPP and possibly TFMPP may induce hypoactivity and hypophagia by an agonist action at central 5-HT$_{1C}$ receptors and that antagonists at these receptors may cause hyperphagia. While hypoactivity due to treatments thought to increase 5-hydroxytryptaminergic function may indicate 5-HT$_{1C}$ receptor activation, a similar conclusion cannot be deduced from hypophagic responses as these can also be mediated by 5-HT$_{1B}$ receptors (Kennett *et al.*, 1987). The possible roles of these receptor types in the anorexic and antidepressant effects of drugs active at 5-HT receptors and in their side-effects are questions of some importance.

We thank pharmaceutical companies for their kind donation of drugs as indicated, and Mrs D. Ranpura for her excellent typing. We also thank the Medical Research Council for financial support.

References

ALOI, J.A., INSEL, T.R., MUELLER, E.A. & MURPHY, D.L. (1984). Neuroendocrine and behavioural effects of m-chlorophenylpiperazine administration in rhesus monkeys. *Life Sci.*, **34**, 1325–1331.

ASARCH, K.E., RANSOM, R.W. & SHIH, J.S. (1985). 5-HT$_{1A}$ and 5-HT$_{1B}$ selectivity of two phenylpiperazine derivatives: evidence for 5-HT$_{1B}$ heterogeneity. *Life Sci.*, **36**, 1265–1273.

BEDARD, P. & PYCOCK, C.K. (1977). 'Wet dog' shake behaviour in the rat: a possible quantitative model of central 5-hydroxytryptamine activity. *Neuropharmacol.*, **16**, 663–670.

BERGEN, S.S. (1964). Appetite stimulating properties of cyproheptadine. *Am. J. Dis. Children*, **108**, 270–273.

BLUNDELL, J.E. (1984). Serotonin and appetite. *Neuropharmacol.*, **23**, 1537–1551.

BLURTON, P.A. & WOOD, M.D. (1986). Identification of multiple binding sites of ^{3}H-5-hydroxytryptamine in the rat CNS. *J. Neurochem.*, **46**, 1392–1398.

BRADLEY, P.B., ENGEL, G., FENIUK, W., FOZARD, J.R., HUMPHREY, P.P.A., MIDDLEMISS, D.N., MYLECHARANE, E.J., RICHARDSON, B.P. & SAXENA, P.R. (1986). Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. *Neuropharmacol.*, **25**, 563–576.

CACCIA, S., FONG, M.H., GARATINI, S. & ZANNINI, M.G. (1982). Plasma concentration of trazodone and 1-(3-chlorphenyl)piperazine in man after a single oral dose of trazodone. *J. Pharm. Pharmacol.*, **34**, 605–606.

CHARNEY, D.S., WOODS, S.W., GOODMAN, W.K. & HENINGER, G.R. (1987). Serotonin function in anxiety II. Effects of the serotonin agonist mCPP in panic disorder patients and healthy subjects. *Psychopharmacol.*, **92**, 14–21.

CLINESCHMIDT, B.V., FLATAKER, L.M., FAISON, E. & HOLMES, R. (1979). An *in vivo* model for investigating α_1 and α_2-receptors in the CNS: studies with mianserin. *Arch. Int. Pharmacodyn.*, **242**, 59–76.

CLOSSE, A. (1983). [^{3}H] mesulergine, a selective ligand for serotonin-2 receptors. *Life Sci.*, **32**, 2485–2495.

DICKINSON, S.L., GADIE, B. & TULLOCH, I.F. (1987). Preclinical *in vivo* assessment of α_2 adrenergic activity in the central nervous system. *Proc. 1st Int. Symp. on Preclin. Strategies in Psychopharmacol.*, Paris, p. 6.

ENGEL, G., GOTHERT, M., HOYER, D., SCHLICKER, E. & HILLENBRAND, K. (1986). Identity of inhibitory presynaptic 5-hydroxytryptamine (5-HT) autoreceptors in the rat brain cortex with 5-HT$_{1B}$ binding sites. *Nauyn-Schmiedebergs Arch. Pharmacol.*, **332**, 1–7.

ENGEL, G., HOYER, D., BERGHOLD, R. & WAGNER, H.

(1981). (±)-[^{125}Iodo]-cyanopindolol, a new ligand for adrenoceptors: identification and quantitation of subclasses of α-adrenoceptors in guinea pig. *Naunyn-Schmiedebergs Arch. Pharmacol.*, **317**, 277–285.

FEIGHNER, J.P. (1980). Trazodone, a triazolopyridine derivative in primary depressive disorder. *J. Clin. Psychiat.*, **41**, 250–255.

GOLDBERG, H.L. & FINNERTY, R.J. (1980). Trazodone in the treatment of neurotic depression. *J. Clin. Psychiat.*, **41**, 430–434.

GREEN, A.R., GUY, A.P. & GARDNER, C.R. (1984). The behavioural effects of RU 24969, a suggested 5-HT, receptor agonist in rodents and the effect on the behaviour of treatment with antidepressants. *Neuropharmacol.*, **23**, 655–661.

HAMON, M., COSSERY, J-M., SPAMPINATO, U. & GOZLAN, H. (1986). Are there selective ligands for 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor binding sites in brain? *Trends Pharmacol. Sci.*, **7**, 336–337.

HEURING, R.E. & PEROUTKA, S.J. (1987). Characterization of a novel 3H-5-Hydroxytryptamine binding site subtype in bovine brain membranes. *J. Neurosci.*, **7**, 894–903.

HOPMAN, H. (1980). Mianserin in out patients with depressive illness in dosage up to 130 mg daily. *Curr. Med. Res. Op.*, **6**, Suppl. 7, 107–114.

HOYER, D., ENGEL, G. & KALKMAN, H.O. (1985). Molecular pharmacology of 5-HT$_1$ and 5-HT$_2$ recognition sites in rat and pig brain membranes: radioligand binding studies with [^{3}H] 5-HT, [^{3}H] 8-OH-DPAT, (−) [^{125}I] iodocyanopindolol, [^{3}H] mesulergine and [^{3}H] ketanserin. *Eur. J. Pharmacol.*, **118**, 13–23.

INVERNIZZI, R., COTECCHIA, S., DE BLASI, A., MENNINI, T., PATACCINI, R. & SAMANIN, R. (1981). Effects of m-chlorophenylpiperazine on receptor binding and brain metabolism of monoamines in rats. *Neurochem. Int.*, **3**, 239–244.

KENNETT, G.A. & CURZON, G. (1987). Evidence that the 5-HT agonists mCPP and TFMPP cause hypolocomotion by stimulating 5-HT$_{1C}$ receptors. *Br. J. Pharmacol. Proc. Suppl.*, **92**, 563p.

KENNETT, G.A., DOURISH, C.T. & CURZON, G. (1987). 5-HT$_{1B}$ agonists induce anorexia at a postsynaptic site. *Eur. J. Pharmacol.*, **141**, 429–435.

LEYSEN, J.E., AWOUTERS, F., KENNIS, L., LADURON, P.M., VANDENBERK, J. & JANSSEN, P.A.J. (1981). Receptor binding profile of R41 468, a novel antagonist of 5-HT2 receptors. *Life Sci.*, **28**, 1015–1022.

LEYSEN, J.E., GOMMEREN, W., VAN GOMPEL, P., WYNANTS, J., JANSSEN, P.F.M. & LADURON, P.M. (1985). Receptor binding properties *in vitro* and *in vivo* of Ritanserin a very potent and long acting serotonin-S$_2$ antagonist. *Molec. Pharmacol.*, **27**, 600–611.

LUCKI, I. & FRAZER, A. (1982). Behavioural effects of indole and piperazine type serotonin receptor agonists. *Soc. Neurosci. Abst.*, **8**, 101.

MIDDLEMISS, D.N. & FOZARD, J.R. (1983). 8-Hydroxy-2-(di-n-propylamino)tetralin discriminates between subtypes of the 5-HT$_1$ recognition site. *Eur. J. Pharmacol.*, **90**, 151–153.

NICKOLSON, V.J., WIERINGA, J.H. & VAN DELFT, A.M.L. (1982). Comparative pharmacology of mianserin, its main metabolites and 6-azamianserin. *Naunyn-Schmiedebergs Arch. Pharmacol.*, **319**, 48–55.

ORTMANN, R. (1984). The 5-HT syndrome in rats as a tool for the screening of psychoactive drugs. *Drug Dev. Res.*, **4**, 593–606.

PAXINOS, G. & WATSON, C. (1982). *The Rat Brain in Stereotaxic Coordinates*. New York: Academic Press.

PAZOS, A., HOYER, D. & PALACIOS, J.M. (1985). The binding of serotoninergic ligands to the porcine choroid plexus; characterization of a new type of serotonin recognition site. *Eur. J. Pharmacol.*, **106**, 539–546.

PAZOS, A. & PALACIOS, J.M. (1985). Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. *Brain Res.*, **346**, 205–230.

PEDIGO, N.W., YAMAMURA, H.I. & NELSON, P.L. (1981). Discrimination of multiple [^{3}H] 5-hydroxytryptamine binding sites by neuroleptic spiperone in rat brain. *J. Neurochem.*, **36**, 220–226.

PEROUTKA, S.J. & SNYDER, S.H. (1979). Multiple serotonin receptors: differential binding of [^{3}H] 5-hydroxytryptamine, [^{3}H] lysergic acid diethylamide and [^{3}H] spiroperidol. *Molec. Pharmacol.*, **16**, 687–699.

PINDER, R.M., BLUM, A., STULEMEIJER, S.M., BARRES, M., MOLCZADZKI, M., RIGAND, A., CHARBAUT, J., ISRAEL, L. & KAMMERER, T. (1980). A double-blind multi-centre trial comparing the efficacy and side effects of mianserin and clomipramine in depressed in-patients and out patients. *Curr. Med. Res. Op.*, **6**, Suppl. 7, 115–122.

PINDER, R.M., BROGDEN, R.N., SAWYER, P.R., SPEIGHT, T.M. & AVERY, G.S. (1975). Fenfluramine: a review of its pharmacological properties and therapeutic efficacy in obesity. *Drugs*, **10**, 241–323.

RICHARDSON, B.P., ENGEL, S., DONATSCH, P. & STADLER, P.A. (1985). Identification of serotonin m-receptor subtypes and their specific blockade by a new class of drugs. *Nature*, **316**, 126–131.

SAMANIN, R., MENNINI, T., FERRARIS, A., BENDOTTI, C., BORSINI, F. & GARATTINI, S. (1979). m-chlorophenylpiperazine: a central serotonin agonist causing powerful anorexia in rats. *Naunyn-Schmiedebergs Arch. Pharmacol.*, **308**, 159–163.

SCATTON, B., DEDEK, J. & ZIVKOVIC, B. (1983). Lack of involvement of α$_2$-adrenoceptors in the regulation of striatal dopaminergic transmission. *Eur. J. Pharmacol.*, **86**, 427–433.

SHEARMAN, G.T. & TOLCSVAI, L. (1987). Effect of the selective 5-HT$_3$ receptor antagonists ICS 205-930 and MDL 72222 on 5-HTP-induced head shaking and behavioural symptoms induced by 5-methoxy-N,N-dimethyltryptamine in rats: comparison with some other 5-HT receptor antagonists. *Psychopharmacol.*, **92**, 520–523.

SILLS, M.A., WOLFE, B.B. & FRAZER, A. (1984). Determination of selective and non-selective compounds for the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes in rat frontal cortex. *J. Pharmacol. Exp. Therap.*, **231**, 480–487.

SMITH, T.M. & SUCKOW, R.F. (1985). Trazodone and m-chlorophenyl-piperazine; concentration in brain and receptor activity in regions in the brain associated with anxiety. *Neuropharmacol.*, **24**, 1067–1071.

SNYDER, S.H. (1980). Tricyclic antidepressant drug interactions with histamine and α-adrenergic receptors. *Pharmakopsychiat.*, **13**, 62–67.

TRICKLEBANK, M.D., FORLER, C. & FOZARD, J.R. (1984). The involvement of subtypes of the 5-HT$_1$ receptor and of catecholaminergic systems in the behavioural response to 8-hydroxy-2-(di-n-propylamino)tetralin in

the rat. *Eur. J. Pharmacol.*, **106**, 271–282.

TRICKLEBANK, M.D., MIDDLEMISS, D.N. & NEILL, J. (1986). Pharmacological analysis of the behavioural and thermoregulatory effects of the putative 5-HT$_1$ receptor agonist RU 24969 in the rat. *Neuropharmacol.*, **25**, 877–886.

(Received June 20, 1987
Revised November 9, 1987
Accepted December 4, 1987)