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5-HT_3 receptor antagonists reverse helpless behaviour in rats

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The effects of the 5-HT_3 receptor antagonists, zacopride, ondansetron and ICS 205-930, were investigated in an animal model of depression, the learned helplessness test. Rats previously subjected to a session of 60 inescapable foot-shocks exhibited a deficit of escape performance in three subsequent shuttle-box sessions. The 5-HT_3 receptor antagonists administered i.p. twice daily on a chronic schedule (zacopride 0.03–2 mg/kg per day; ondansetron and ICS 205-930: 0.125–2 mg/kg per day) reduced the number of escape failures at low to moderate daily doses. This effect was not observed with the highest dose(s) of zacopride, ondansetron and ICS 205-930 tested. These results indicate that 5-HT_3 antagonists may have effects like those of conventional antidepressants in rats.

5-HT_3 receptor antagonists; Learned helplessness paradigm; (Rat)

1. Introduction

Brain binding sites have been previously identified for both the 5-HT_1 and 5-HT_2 subtypes. More recently, the existence of 5-HT_3 receptors has been demonstrated in rat and human brain (see Watling, 1988). The functional correlates for these sites are not yet understood. Various reports indicate that 5-HT_3 receptor antagonists might alter, over a large dose range, the behaviour of rodents and monkeys in a manner consistent with that of anxiolytic drugs (Costall et al., 1987, 1988; Jones et al., 1988; Piper et al., 1988; Glenn and Green, 1989; Papp and Przegalinski, 1989). In addition, 5-HT_3 receptor antagonists have been shown to reduce dopamine (DA)-mediated hyperactivity responses, indicating that these compounds might also have potential antipsychotic activity (see Tricklebank, 1989). Finally, a recent report suggests that 5-HT_3 receptor antagonists might improve animal performances in cognition tests (Barnes et al., 1990).

Despite some conflicting results, the involvement of serotonin transmission in depressive-like behaviour in animals and in the activity of antidepressant drugs is generally accepted (see Willner, 1990 for a review). Indeed, 5-HT_{1A} agonists and 5-HT_2 receptor antagonists have been found to reduce the escape deficit in the learned helplessness test, an animal model of depression highly sensitive to antidepressant drugs, as did conventional antidepressants and 5-HT uptake blockers (Giral et al., 1988; Martin et al., 1990a, c). In contrast, 5-HT_{1B} receptor agonists failed to reverse helpless behaviour (Martin and Puech, 1991). The aim of the present study was to examine the effect of 5-HT_3 receptor antagonists on this behavioural deficit. The effects of three 5-HT_3 receptor antagonists, zacopride (4-amino-N-1-azabicyclo(2.2.2)oct-3-yl-5-chloro-2-methoxybenzamide), ondansetron (GR 38032F; 1,2,3,9-tetrahydro-9-methyl-3[(C2-methyl-1H-imidazol-1yl)methyl]-4H-carbazol-4-one) and ICS 205-930 ((3α-tropanyl)-1H-indole-3-carboxylic acid ester), were therefore investigated with the learned helplessness test in the rat. The results described here were presented in preliminary form at the International Symposium on Serotonin from Cell Biology to Pharmacology and Therapeutics, Florence, March 29 to April 1, 1989 (Martin et al., 1989).

2. Materials and methods

2.1. Animals

The experiments were carried out on male Wistar A.F. rats (Centre d'Elevage R. Janvier, France) with an initial weight of 180–200 g. The animals were housed

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in groups of 10/cage under standard conditions: room temperature (21 ± 1°C); light/dark cycle (12 h/12 h); water and food were available ad libitum.

2.2. Apparatus and experimental procedure

2.2.1. Learned helplessness procedure

The procedure has been described earlier (Martin et al., 1986). Briefly, it includes two phases.

2.2.1.1. Helplessness induction (inescapable shock preconditioning). Inescapable electric foot-shocks were delivered to each rat in a Plexiglas chamber (20 × 10 × 10 cm) covering a stainless-steel grid. A constant-current shocking device was used to deliver 60 scrambled randomized, inescapable shocks (0.8 mA, D.C.; 15 s duration, every min ± 15 s) to the grid floor. Control rats were placed in identical chambers for 1 h but no shocks were administered. Helplessness was induced in the morning on day 1

2.2.1.2. Conditioned avoidance training. To evaluate escape deficits, avoidance training was initiated 48 h (day 3) after inescapable shock preconditioning in automated two-way shuttle-boxes (60 × 21 × 30 cm) with a floor consisting of stainless-steel rods spaced 1.0 cm apart. Each shuttle-box was divided into two chambers of equal size by a partition with a gate giving access to the adjacent compartment through a 7 × 7 cm space. The animals were placed singly in the shuttle-box and allowed to habituate to the environment for 5 min (for the first session only) and then were subjected to 30 avoidance trials (intertrial intervals of 30 s). A light signal was presented during the first 3 s of each trial, allowing the animals to avoid shocks by moving to the other side of the box (avoidance response). If a response did not occur within this period, a 0.8 mA shock was applied to the grid floor. If no response occurred during the 3-s shock presentation (escape response), the shock and the light signal were terminated automatically. Shuttle-box sessions were performed for 3 consecutive days (days 3, 4 and 5) in the morning. The number of escape failures, referred to as a 'no crossing response' during the stimuli presentation, the number of escape responses and the number of avoidance responses were recorded during each shuttle-box session.

2.3. Drug administration

Drugs were injected i.p. on 5 consecutive days, i.e. 6 h after inescapable shocks on day 1 and then twice a day in the morning (30 min before shuttle-box sessions) and between 18 h and 19 h. For all drugs, half the daily dose was given at each injection, except on day 1 when the daily dose was given as a single bolus. The three 5-HT_3 receptor antagonists were studied in independent experiments. Rats were treated randomly according to one of the following protocols. Rats pre-exposed to inescapable shocks were given zacopride (Delalande): 0.03–2 mg/kg per day (n = 8–10), ondansetron (Glaxo): 0.125–2 mg/kg per day (n = 8–13) or ICS 205-930 (Sandoz): 0.125–2 mg/kg per day (n = 8–9). Control rats receiving inescapable shocks were injected with distilled water (n = 30, 30 and 10, for experiments with zacopride, ondansetron and ICS 205-930, respectively). Four groups of rats not pre-exposed to inescapable shocks were injected with the daily dose of 2 mg/kg of zacopride (n = 8), ondansetron (n = 6) or ICS 205-930 (n = 6) or with distilled water (n = 19), and two additional groups of non-shocked rats were given 0.125 mg/kg per day of zacopride (n = 8), or distilled water (n = 6). Drugs were dissolved in distilled water and injected in a volume of 0.5 ml/100 g body weight.

2.4. Statistical analyses

The results were expressed as mean (±S.E.M.) numbers of escape failures recorded over 30 trials during each shuttle-box session and mean (±S.E.M.) total numbers of avoidance and escape responses during the three shuttle-box sessions (90 trials). Between-group comparisons were performed using a one-way analysis of variance (ANOVA) with drug-dose as the independent factor, and the two-tailed Dunnett's t-test.

3. Results

As previously described (Martin et al., 1986), vehicle-injected rats pre-exposed to inescapable shocks exhibited more escape failures than did the controls without inescapable shocks (18–22 escape failures vs. 5–12 depending on the groups and on the shuttle-box sessions; $P < 0.01$). The most pronounced differences were usually observed during the third shuttle-box session (data not shown).

Zacopride induced an overall reduction of the number of escape failures during each of the three shuttle-box sessions ($F(7,88) = 3.98$, 6.88 and 13.59 for sessions 1, 2 and 3, respectively, $P < 0.001$ for each session). During the first shuttle-box session, the reversal of escape failures reached a statistically significant level for only one dose of zacopride (0.125 mg/kg per day; $t(8,88) = 3.74$; $P < 0.01$). During the second and the third shuttle-box sessions, the number of escape failures was significantly reduced by doses ranging from 0.06 to 0.5 mg/kg per day (smallest $t(8,88) = 3.51$; $P < 0.01$) (fig. 1A). Conversely, the total number of escape responses was significantly enhanced ($F(7,88) = 10.05$; $P < 0.001$) and posthoc analysis indicated that this effect reached statistical significance for the doses of 0.06, 0.125, 0.25 and 0.5 mg/kg per day. In contrast,

the number of avoidance responses was not significantly modified by zacopride (see table 1).

Ondansetron induced an overall reduction of the number of escape failures during the second and third shuttle-box sessions ($F(5,79) = 2.37$, $P < 0.05$ and 5.66, $P < 0.001$ for sessions 2 and 3, respectively). During the second shuttle-box session the reversal of escape failures reached a statistically significant level for only one dose of ondansetron (0.5 mg/kg per day; $t(6,79) = 3.17$; $P < 0.01$). During the third shuttle-box session, the number of escape failures was significantly reduced by 0.25 mg/kg per day ($t(6,79) = 3.17$; $P < 0.01$) and 0.5 mg/kg per day ($t(6,79) = 4.51$; $P < 0.01$) (fig. 1B). The total number of escape responses was significantly increased ($F(5,79) = 3.87$; $P < 0.05$) and posthoc analysis showed that this was due to a significant effect at 0.5 mg/kg per day. The number of avoidances was not significantly modified by ondansetron (see table 1).

ICS 205-930 induced an overall reduction of the number of escape failures during the third shuttle-box session ($F(3,31) = 2.99$; $P < 0.05$) The reversal of escape failures reached a statistically significant level for only one dose of ICS 205-930 (0.5 mg/kg per day; $t(4,31) = 2.80$; $P < 0.05$) (fig. 1C). The total number of escape responses was significantly enhanced ($F(3,31) = 3.15$; $P < 0.05$) and posthoc analysis indicated that this was due to a significant effect at 0.5 mg/kg per day. The number of avoidance responses was not modified by ICS 205-930 (see table 1). In rats pre-exposed to inescapable shocks, the highest daily dose(s) of each compound (1 and 2 mg/kg per day for zacopride or

TABLE 2

Lack of effect of 5-HT_3 antagonists on the ability of rats *not* pre-exposed to inescapable shocks to escape or avoid electric shocks during the three shuttle-box sessions.

All results were non-significant (ANOVA). n = number of rats.

Drugs	Dose mg/kg per day	n	Number (mean ± S.E.M.) of responses during the three shuttle-box sessions (SB) per 30 trials		
			SB1 (day 3)	SB2 (day 4)	SB3 (day 5)
			Escape failures		
Rats without inescapable shocks					
Control	0	19	9.5 ± 1.0	9.3 ± 1.1	8.0 ± 1.2
Zacopride	2	8	11.3 ± 1.2	10.0 ± 1.8	8.9 ± 1.8
Ondansetron	2	6	10.5 ± 1.3	10.0 ± 1.7	7.5 ± 1.4
ICS 205-930	2	6	8.3 ± 2.0	6.8 ± 1.0	7.2 ± 1.4
			Avoidance responses		
Rats without inescapable shocks					
Control	0	19	0.5 ± 0.2	0.8 ± 0.2	0.9 ± 0.3
Zacopride	2	8	0.6 ± 0.3	0.1 ± 0.1	0.6 ± 0.3
Ondansetron	2	6	0.2 ± 0.2	0.5 ± 0.3	0.7 ± 0.3
ICS 205-930	2	6	0.7 ± 0.5	0.8 ± 0.5	0.7 ± 0.5
Control	0	6	0.5 ± 0.3	0.8 ± 0.5	1.7 ± 0.7
Zacopride	0.125	8	0.5 ± 0.2	0.8 ± 0.5	1.0 ± 0.7

TABLE 1

The number of avoidance responses during the three shuttle-box sessions in rats pre-exposed to inescapable shocks.

All results were non significant for all groups treated, as compared to the respective vehicle-injected rats (control) (ANOVA). n = number of rats.

Drugs	Dose mg/kg per day	n	Number (mean ± S.E.M.) of avoidance responses during the three shuttle-box sessions (SB) per 30 trials		
			SB1 (day 3)	SB2 (day 4)	SB3 (day 5)
Rats with inescapable shocks					
Control	0	30	0.4 ± 0.2	0.6 ± 0.4	0.8 ± 0.5
Zacopride	0.03	8	0.1 ± 0.1	0.1 ± 0.1	0
	0.06	8	0.9 ± 0.6	1.5 ± 0.7	1.3 ± 0.6
	0.125	10	0.3 ± 0.2	0.6 ± 0.2	0.7 ± 0.3
	0.25	10	0.5 ± 0.3	0.5 ± 0.3	0.3 ± 0.2
	0.5	10	0.3 ± 0.2	2.1 ± 0.8	0.9 ± 0.3
	1.0	10	0.3 ± 0.2	0.3 ± 0.2	0.6 ± 0.3
	2.0	10	0.1 ± 0.1	0.3 ± 0.2	0
Control	0	30	0.6 ± 0.2	0.7 ± 0.4	0.5 ± 0.4
Ondansetron	0.125	13	0.5 ± 0.2	0.5 ± 0.3	0.2 ± 0.2
	0.25	8	0.4 ± 0.4	0.1 ± 0.1	0.5 ± 0.4
	0.5	13	0.5 ± 0.2	0.3 ± 0.2	0.1 ± 0.1
	1.0	8	0.1 ± 0.1	0.3 ± 0.2	0.8 ± 0.3
	2.0	13	1.6 ± 0.9	0.5 ± 0.3	1.2 ± 0.7
Control	0	10	0.3 ± 0.2	0.4 ± 0.4	0.2 ± 0.2
ICS 205-930	0.125	9	0.4 ± 0.3	0.9 ± 0.6	0.8 ± 0.4
	0.5	9	0.7 ± 0.2	1.0 ± 0.9	1.2 ± 0.6
	2.0	8	0.1 ± 0.1	0.3 ± 0.3	0

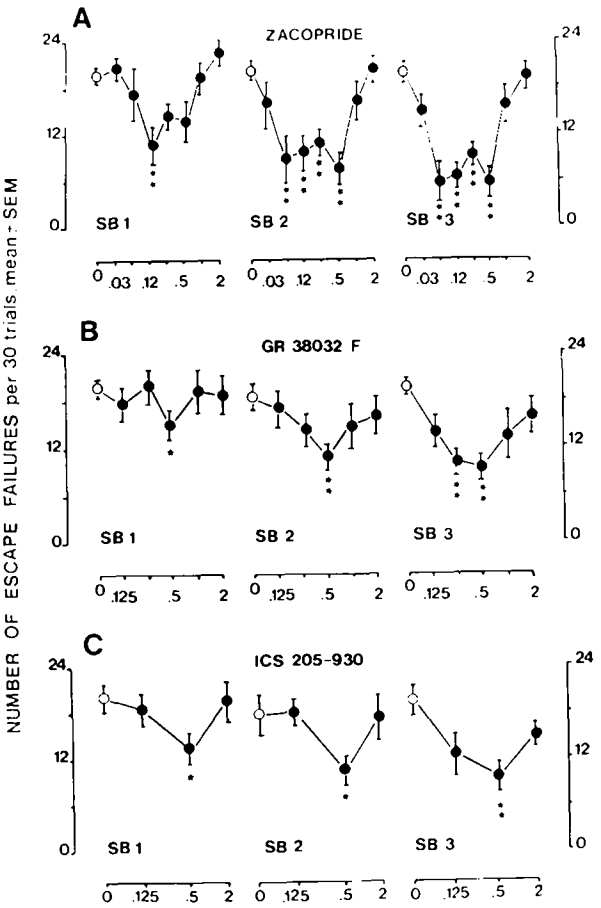

Fig. 1. Reversal by zacopride, ondansetron (GR 38032F) and ICS 205-930 of helpless behavior (escape failures). The data are the mean number (±S.E.M.) of escape failures during each of the three consecutive daily shuttle-box sessions (SB) (days 3, 4, 5). Escape failures refer to failure of the rat to change compartments during the electric foot-shocks (30 trials per session). Stars indicate that after pre-exposure to inescapable shocks the response of treated rats (●) differed significantly from that of vehicle-injected animals (○) at * $P < 0.05$ and ** $P < 0.01$ (Dunnett's t-test after ANOVA).

ondansetron and 2 mg/kg per day for ICS 205-930) failed to reduce the number of escape failures significantly during the three shuttle-box sessions (fig. 1A, B, C).

Additional experiments were performed in order to test whether the lack of effect of the highest daily doses in helpless rats was not due to a deleterious action. Thus, the performance of rats not pre-exposed to inescapable shocks (avoidance responses and escape failures) was not significantly modified by zacopride, ondansetron or ICS 205-930 (2 mg/kg per day) as compared to that of vehicle-injected animals (table 2). In addition, an 'active' dose of zacopride (0.125 mg/kg per day) to rats *without* inescapable shocks did not significantly modify the ability to escape or to avoid electric shocks in avoidance sessions (see table 2).

4. Discussion

This study showed that three chemically different 5-HT_3 receptor antagonists (zacopride, ondansetron and ICS 205-930) administered twice daily after a session of inescapable foot-shocks reversed the escape deficits typically observed in subsequent shuttle-box training. This type of effect is usually induced by various antidepressants administered according to a comparable procedure (Sherman et al., 1982; Martin et al., 1986, 1990c). This suggests that 5-HT_3 receptor antagonists at low to moderate doses (i.e., 0.06–0.5 mg/kg per day) exert antidepressant-like activity. Such an effect could not be accounted for by non-specific phenomena since the rats did not exhibit any signs of excitation. Inter-trial crossings, in particular, were not increased at doses that prevented escape deficits (results not shown).

At the highest dose(s) studied (1 or 2 mg/kg per day), the three 5-HT_3 receptor antagonists no longer reduced the escape deficit in rats pre-exposed to inescapable shocks. Such doses did not induce sedation or other signs of physical disability. In addition, the ability of rats *not pre-exposed* to inescapable shock to escape in the shuttle-box training was not impaired by a high dose (2 mg/kg per day) of any of the compounds. This indicates that non-specific or debilitating effects are unlikely to mask any antidepressant-like activity of these high doses. While similar biphasic dose–effect relationships were reported after acute administration of various 5-HT_3 receptor antagonists in different tests for anxiolytic activity (Costall et al., 1987; Jones et al., 1988), these biphasic dose-response curves still remain unexplained.

It is possible that the reduction of helpless behaviour results directly or indirectly from impaired 5-HT transmission. However, it has been proposed that decreased serotoninergic activity may increase vulnerability to affective disorders or may produce depression (Murphy et al., 1978). Clinical trials have indicated that drugs blocking serotonin uptake, which increase 5-HT transmission, such as citalopram, fluvoxamine and fluoxetine, are effective antidepressants. Furthermore, similar antidepressant activities have been described for 5-HT_{1A} agonists in both man and animals (Giral et al., 1988; Martin et al., 1990a; Robinson et al., 1990 and Martin et al., in press for review). Several reports indicate that the effects of 5-HT_{1A} agonists are more likely to result from direct stimulation of post-synaptic receptors (Martin et al., 1990a; Schreiber and De Vry, 1990) than from reduction of 5-HT activity. 5-HT_2 receptor antagonists also induce reversal of helpless behaviour in this test (Martin et al., 1990c). However, it is not clear whether this action is related to 5-HT_2 receptors or can result from the blockade of 5-HT_{1C} sites, since several 5-HT_2 receptor antagonists can act

as 5-HT_{1C} receptor antagonists. However, it is also possible that a functional interaction between central 5-HT_2 and 5-HT_1 receptors mediates the increase in 5-HT transmission. In addition, the reversal of helpless behaviour by antidepressants was frequently related to a net *increase* in 5-HT transmission (Martin et al., 1990c). Thus, the antidepressant-like effects of 5-HT drugs in the learned helplessness test seem unlikely to be accounted for by a global impairment of 5-HT transmission. It is possible that imbalance between the different 5-HT receptor subtypes and/or other receptors could underlie the reversal of helpless behaviour.

As mentioned above, several 5-HT receptor subtypes could participate in the reduction of helpless behaviour. The effects of the 5-HT_3 receptor antagonists, however, are unlikely to be mediated by one of the other binding sites since zacopride, ondansetron and ICS 205-930 are poorly recognized by both hippocampal and cortical 5-HT_{1A} and 5-HT_2 receptors (Jones et al., 1988; Gozlan, unpublished results).

Evidence indicates that central neurotransmitter impairment may contribute to the induction of helpless behaviour and that enhanced neurotransmission of certain neuromediators plays a crucial role in mediating the effect of antidepressant drugs (Anisman et al., 1981; Hamilton et al., 1986; Martin et al., 1987). It is possible that neurotransmitters (e.g., NAD or DA) are indirectly involved in the ability of 5-HT_3 receptor antagonists to reverse helpless behaviour. Feuerstein and Hertting (1986) were the first to show an effect of the 5-HT_3 receptor antagonists on neurotransmitter release. They showed that the stimulatory effect of 5-HT on [^{3}H]NAD release was reversed by high doses of MDL 72222 and ICS 205-930. Blandina et al. (1988) then showed that 5-HT and 2-methyl-5-HT could stimulate the release of dopamine from striatal slices; this effect was blocked competitively by low concentrations of 5-HT_3 receptor antagonists. Recently, Imperato et al. (1990) showed that stress activation of limbic and cortical dopamine release is prevented by ICS 205-930. Additionally, Barnes et al. (1989) have shown that 5-HT_3 receptor receptors modulate the inhibition of K^+-stimulated [^{3}H]acetylcholine release from rat entorhinal cortex. The behavioural deficit induced by inescapable shocks has however been proposed to result from cognitive changes (Maier and Seligman, 1976). Ondansetron has been shown to improve performance in rodent and primate tests of cognition (Barnes et al., 1990). The improved performance in shocked rats could thus result from a cognitive enhancing activity of 5-HT_3 receptor antagonists. However, zacopride, at a dose that completely reverses the helpless behaviour induced by inescapable shock, did not improve overall performance in unshocked rats (without inescapable shock). Furthermore, the three compounds at doses active to reduce the escape deficit failed to enhance avoidance responses in these experimental conditions. The reduction of behavioural deficits in the learned helplessness test by 5-HT_3 receptor antagonists thus seems unlikely to be due to enhanced cognitive functions.

This hypothesis, however, cannot ruled out completely. The possibility cannot be excluded that escape deficits in shocked rats reflect specific deterioration of cognitive ability sensitive to 5-HT_3 receptor antagonists. Conversely, these compounds could have no effect on basal performance or on performance requiring higher functions of learning, memory or information processing such as those necessary to learn to avoid shocks.

Furthermore, it remains uncertain whether the effect now seen in the learned helplessness test reflects an anxiolytic action because classical anxiolytic drugs such as benzodiazepines, and imidazopyridines such as alpidem have been found to be unable to reduce helpless behaviour (Sherman et al., 1982; Martin et al., 1990b, and Martin personal communication). Some evidence for central effects of these drugs was obtained from non-traditional models of anxiety in animals (Costall et al., 1987, 1988; Jones et al., 1988; Piper et al., 1988; Glenn and Green, 1989; Papp and Przegalinski, 1989). In addition, the doses effective to produce anxiolytic-like effects in rodents and marmosets were usually considerably lower than the doses reversing helpless behaviour in the present study.

Other studies are needed to show whether there is cooperativity between the various 5-HT receptors and whether the behavioural effects observed are definitely mediated via 5-HT_3 receptors.

In conclusion, the results of several behavioural studies have indicated a potential use for 5-HT_3 receptor antagonists in various psychiatric disorders. However, the therapeutic effects of 5-HT_3 receptor antagonists still need to be demonstrated in clinical practice. Reversal of escape deficit in animals could possibly be used to predict potential therapeutic activity in depressive states in man.

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References

Anisman, H., M. Rich and L.S. Sklar, 1981, Noradrenergic and dopaminergic interaction in escape behavior analysis of uncontrollable stress effects, Psychopharmacology 74, 263.

Barnes, J.M., N.M. Barnes, B. Costall, R.J. Naylor and M.B. Tyers, 1989, 5-HT_3 receptor mediate inhibition of acetylcholine release in cortical tissue, Nature 338, 762.

Barnes, J.M., B. Costall, J. Coughlan, A.M. Domeney, P.A. Gerrard, M.E. Kelly, R.J. Naylor, E.S. Onaivi, D.M. Tomkins and M.B. Tyers, 1990, The effects of ondansetron, a 5-HT_3 receptor antagonist, on cognition in rodents and primates, Pharmacol. Biochem. Behav. 35, 955.

Blandina, P., J. Goldfarb and J.P. Green, 1988, Activation of a 5-HT_3 receptor releases dopamine from rat striatal slice, Eur. J. Pharmacol. 155, 349.

Costall, B., A.M. Domeney, P.A. Gerrard, M.E. Kelly, R.J. Naylor and M.B. Tyers, 1987, Effects of the 5-HT_3 receptor antagonists GR38032F, ICS 205-930 and BRL 43694 in tests for anxiolytic activity, Br. J. Pharmacol. 91, 195P.

Costall, B., A.M. Domeney, P.A. Gerrard, M.E. Kelly and R.J. Naylor, 1988, Zacopride: anxiolytic profile in rodent and primate models of anxiety, J. Pharm. Pharmacol. 40, 302.

Feuerstein, T.J. and G. Hertting, 1986, Serotonin (5-HT) enhances hippocampal noradrenaline (NA) release: evidence for facilitatory 5-HT receptors within the CNS, Naunyn-Schmiedeb. Arch. Pharmacol. 333, 191.

Giral, P., P. Martin, P. Soubrié and P. Simon, 1988, Reversal of helpless behavior in rats by putative 5-HT_{1A} agonists, Biol. Psychiat. 23, 237.

Glenn, B. and S. Green, 1989, Anxiolytic profile of GR 38032F in the potentiated startle paradigm, Behav. Pharmacol. 1, 91.

Hamilton, M.E., R.M. Zacharko and H. Anisman, 1986, Influence of p-chloroamphetamine and methysergide on the escape deficits provoked by inescapable shock, Psychopharmacology 90, 203.

Imperato, A., S. Puglisi-Allegra, A. Zocchi, M.G. Scrocco, P. Casolini and L. Angelucci, 1990, Stress activation of limbic and cortical dopamine release is prevented by ICS 205-930 but not by diazepam, Eur. J. Pharmacol. 175, 211.

Jones, B.J., B. Costall, A.M. Domeney, M.E. Kelly, R.J. Naylor, N.R. Oakley and M.B. Tyers, 1988, The potential anxiolytic activity of GR 38032F, a 5-HT_3 receptor antagonist, Br. J. Pharmacol. 93, 985.

Maier, S.F. and M.E.P. Seligman, 1976, Learned helplessness: Theory and evidence, J. Exp. Psychol. Gen. 105, 3.

Martin, P., J.M. Chignon and A.J. Puech, A new class of antidepressant drugs: The 5-HT_{1A} agonists – A review – , Neuropsychopharmacology (in press).

Martin, P., R.J. Beninger, M. Hamon and A.J. Puech, 1990a, Antidepressant-like action of 8-OH-DPAT, a 5-HT_{1A} agonist, in the learned helplessness paradigm: evidence for a postsynaptic mechanism, Behav. Brain Res. 38, 135.

Martin, P., J. Massol, J.P. Belon, G. Gaudel and P. Soubrié, 1987, Thyroid function and reversal by antidepressant drugs of depressive-like behavior (escape deficits) in rats, Neuropsychobiology 18, 21.

Martin, P., J. Massol, J.M. Chignon and A.J. Puech, 1990b, Effects of benzodiazepines on reversal by tricyclics or serotonin uptake blockers of depressive-like behavior in rodents, Fund. Clin. Pharmacol. 4, 428.

Martin, P., A. Moulignier, D. Brochet, H. Gozlan and A.J. Puech, 1989, Are the 5-HT_3 antagonists antidepressant drugs?, International Symposium on Serotonin from cell biology to Pharmacology and Therapeutics, Florence (Italy), March 29 to April 1, 1989.

Martin, P. and A.J. Puech, 1991, Is there a relationship between 5-HT_{1B} receptors and the mechanisms of action of antidepressant drugs in the learned helplessness paradigm in rats, Eur. J. Pharmacol. 192, 193.

Martin, P., P. Soubrié and A.J. Puech, 1990c, Reversal of helpless behavior by serotonin uptake blockers in rats, Psychopharmacology 101, 103.

Martin, P., P. Soubrié and P. Simon, 1986, Shuttle-box deficits induced by inescapable shocks in rats: reversal by the beta-adrenoceptor stimulants clenbuterol and salbutamol, Pharmacol. Biochem. Behav. 24, 177.

Murphy, D.L., I. Campbell and J.L. Costa, 1978, Current status of the indoleamine hypothesis of affective disorders, in: Psychopharmacology: a Generation of Progress, eds. M.A. Lipton, P. Di Mascio and K.F. Killam (Raven Press, New York) p. 1234.

Papp, M. and E. Przegalinski, 1989, The 5-HT_3 receptor antagonists ICS 205-930 and GR38032F, putative anxiolytic drugs, differ from diazepam in their pharmacological profile, J. Psychopharmacol. 3, 14.

Piper, D., N. Upton, D. Thomas and J. Nicholass, 1988, The effects of the 5-HT_3 receptor antagonists BRL 43694 and GR 38032F in animal behavioural models of anxiety, Br. J. Pharmacol. 95, 314P.

Robinson, D.S., K. Rickels, J. Feighner, L.F. Fabre, R.E. Gammans, R.C. Schrotriya, D.R. Alms, J.J. Andary and M.E. Messina, 1990, Clinical effects of the 5-HT_{1A} partial agonists in depression, J. Clin. Psychopharmacol. 10, 67S.

Schreiber, R. and J. De Vry, 1990, Neuro-anatomical correlate of the antidepressant-like effects of ipsapirone and 8-OH-DPAT in the rat forced swimming test, Psychopharmacology 101, S52.

Sherman, A.D., J.L. Sacquitne and F. Petty, 1982, Specificity of the learned helplessness model of depression, Pharmacol. Biochem. Behav. 1, 449.

Tricklebank, M.D., 1989, Interactions between dopamine and 5-HT3 receptors suggest new treatments for psychosis and drug addiction, Trends Pharmacol. Sci. 10, 127.

Watling, K.J., 1988, Radioligand binding studies identify 5-HT_3 recognition sites in neuroblastoma cell lines and mammalian CNS, Trends Pharmacol. Sci. 9, 227.

Willner, P., 1990, Animal models of depression: an overview, Pharmacol. Ther. 45, 425.