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Differences between 5-HT_3 receptor antagonists in modulation of visceral hypersensitivity

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1 Noxious colo-rectal distension was applied in conscious rats by acute balloon inflation and the effects observed as abdominal muscle contraction with the threshold typically between 10–40 mmHg. The effects of 5-HT_3 receptor antagonists on responses to noxious colo-rectal distension were then studied in both normal rats and those pretreated with 5-hydroxytryptophan (5-HTP).

2 Granisetron and ondansetron (10 $\mu g\,kg^{-1}$ and 1 $mg\,kg^{-1}$, s.c.) had no effect on visceromotor thresholds to colo-rectal distension in normal rats.

3 Hypersensitivity of the colo-rectum was achieved by systemic administration of a low dose of 5-HTP (10 $mg\,kg^{-1}$, s.c.) which lowered the distension pressure required to induce the visceromotor reflex; analysis of variance showed a highly significant treatment effect ($F_{1,11} = 84.26$, $P<0.001$).

4 Granisetron, zatosetron, bemesetron and renzapride equi-potently increased the threshold values at which distension evoked a visceromotor reflex after dosing with 5-HTP, with a maximal response 3.6 to 4.2 fold above saline controls, at 10 $\mu g\,kg^{-1}$, s.c. Metoclopramide (10 $\mu g\,kg^{-1}$) also raised the level of distension required to elicit a response. By comparison, tropisetron caused a small, non-significant increase in visceromotor threshold values and only at high doses (1 $mg\,kg^{-1}$), whilst ondansetron and BRL 46470 had no signficant effects at doses up to 10 $mg\,kg^{-1}$.

5 The response to granisetron (10 $\mu g\,kg^{-1}$, s.c.) in 5-HTP-treated rats was unaltered by pre-administration of naloxone (5 $mg\,kg^{-1}$, s.c.).

6 These results suggest that a 5-HT_3-like receptor modulates 5-HTP- evoked visceral hypersensitivity. However, the rank order of antagonist potency does not correlate with their order of potency against the classically defined 5-HT_3 receptor.

Keywords: 5-HT_3 receptors; antagonists; colo-rectal distension; visceral pain; 5-hydroxytryptamine (5-HT)

Introduction

Studies in the anaesthetized rat using acute levels of noxious colo-rectal or duodenal distension have demonstrated both pressor and depressor blood pressure pseudoaffective reflexes (Ness & Gebhart, 1988; Moss & Sanger, 1990). Of these cardiovascular pseudoaffective reflexes, the depressor response was found to be inhibited by the 5-HT_3 receptor antagonists, granisetron and ondansetron, the latter showing only weak activity (Moss & Sanger, 1990; Banner & Sanger, 1991). As a consequence of these findings, granisetron was tested clinically as a potential visceral analgesic agent since pain and related gastrointestinal sensations are one of the diagnostic features of Irritable Bowel Syndrome (IBS; Thompson *et al.*, 1992). Prior & Read (1993) investigated the analgesic potential of granisetron in IBS patients with bowel hypersensitivity and they found that granisetron raised the thresholds for sensations elicited by rectal distension.

Ness & Gebhart (1988, 1990) have described an experimental model using conscious rats, in which a visceromotor reflex is monitored as an indication of noxious levels of colo-rectal distension (CRD). However, using this model Danzebrink & Gebhart (1991) found that the 5-HT_3 receptor agonist, 2-methyl-5-hydroxytryptamine (2-methyl-5-HT) when administered intrathecally was antinociceptive and that its ability to raise visceromotor thresholds was prevented by pretreatment with the selective antagonist, bemesetron. When administered intrathecally, the antagonist alone had no effect on visceromotor thresholds. Similar results were obtained by Glaum *et al.* (1990) in a standard nociceptive model when they used intrathecal 2-methyl-5-HT to inhibit the tail flick reflex in rats and subsequently prevented this response with bemesetron.

The apparently conflicting data obtained with 5-HT_3 receptor antagonists in different experimental models made it necessary to determine if the action of the 5-HT_3 receptor antagonists seen in the anaesthetized rat model and in IBS patients could be obtained in conscious rats. Therefore, the conscious CRD model was modified to study the effect of the antagonists in both normal rats and in rats in which the visceral hypersensitivity of IBS patients was mimicked by systemic administration of the precursor to 5-HT, 5-hydroxytryptophan (5-HTP).

Methods

Male Wistar rats (200–500 g) were fasted individually overnight to promote emptying of the colo-rectum. Under halothane anaesthesia a 6–7 cm long latex balloon was inserted intra-anally to a position approximately 1 cm beyond the ano-rectal verge. The animals were allowed to recover. The cannula from the balloon, which was taped to the tail to prevent expulsion of the balloon, was connected to a pressure transducer linked to a pen recorder and via a 3-way tap to a peristaltic pump. Throughout the procedure the singly housed animals were allowed unrestricted movement. After full recovery the rats were dosed subcutaneously (s.c.) with either, 5-HTP (10 $mg\,kg^{-1}$ and 25 $mg\,kg^{-1}$) or saline vehicle. At 5 min a ramp inflation of the colo-rectal balloon was performed until the visceromotor threshold was observed, within 40 s. This is seen as abdominal muscle contraction and at this point the stimulus was immediately removed by opening the 3-way tap to air until the following inflation. The threshold value was noted from the pen recorder. This inflation procedure was repeated at 5 min intervals. It had previously been found that electromyographic recording and

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visualisation of abdominal muscle contraction gave the same results (unpublished observations), which is in agreement with Ness & Gebhart (1988). 5-HT$_3$ receptor antagonists or saline were given s.c. after 3 stable responses to noxious CRD were achieved and within 45 min of 5-HTP dosing. The distensions were then performed at 5 min intervals for a further 30 min. If, at any time, the distension pressure reached 100 mmHg without observation of the visceromotor reflex then that inflation procedure was terminated and the stimulus removed. The experimental procedure was repeated twice in the animals at an interval of at least one week.

Changes in distension pressure were compared with the mean of the predose stable recordings which was taken to be 100%. The maximum effect in the presence of the antagonist at any time point within the 30 min post-dose period was used for the construction of dose effect-curves. The maximum threshold responses in the presence of the antagonists were then compared as a ratio against the maximum response obtained after dosing with saline, this increase being assigned the value of 1.0. The results represent the mean and standard error of the mean and were compared by Student's t test where raw data were analysed. Analysis of variance using a repeated measures design was also used.

5-Hydroxy-L-trytophan, cisapride, morphine sulphate, naloxone hydrochloride were obtained from Sigma, Janssen Pharmaceuticals, Evans Medical and Endo Laboratories Inc. respectively. Granisetron, BRL 46470A (endo-N-(8-methyl-8-azabicyclo [3.2.1] oct-3yl)-2,3-dihydro-3,3-dimethyl-indole-1-carboxamide HCl), bemesetron (MDL 72222), tropisetron (ICS 205-930), metoclopramide, renzapride, ondansetron, quipazine maleate and zatosetron, were synthesized by SB Pharmaceuticals. All drugs were administered s.c. with 0.9% w/v saline as vehicle and at a volume equivalent to 1 ml kg^{-1} body weight.

Results

Visceromotor threshold values in both 5-HTP-treated and vehicle-treated animals lay in the range of 10–40 mmHg. Morphine (10 μg kg^{-1}) was administered to demonstrate that the visceromotor threshold in response to noxious levels of colo-rectal distension could be altered by an analgesic agent. Thus at this dose morphine caused a maximum increase above stable pre-dose control pressures of 153.1 ± 80.8%, $n = 5$, compared to a maximum increase of 18.8 ± 3.1%, $n = 11$, after dosing with saline. At 100 μg kg^{-1} morphine caused the distension pressure to reach the cut off level at which the stimulus was removed.

5-HTP did not demonstrate any antinociceptive properties. Rather, it was found that 5-HTP lowered the threshold to noxious levels of distension. Figure 1 shows that whilst the vehicle had no effect on levels of CRD required to evoke a visceromotor reflex, 5-HTP (10 mg kg^{-1}) reduced the visceromotor threshold, within 10 min, to a minimum of 52.8 ± 4.9% ($n = 13$) of predose values. Analysis of variance using repeated measures showed a highly significant effect with 5-HTP treatment when compared with saline controls ($F_{1,11} = 84.26$, $P<0.001$). As can be seen in Figure 1 there was a time-dependent onset of maximal activity after 5-HTP treatment (treatment × time $F_{11,121} = 6.07$, $P<0.001$). A further lowering of the visceromotor threshold was achieved by increasing the dose of 5-HTP to 25 mg kg^{-1}; the distension pressure then required to elicit a response was only 34.6 ± 9.6% ($n = 5$) of predose control values. However, in separate experiments (not presented here) this higher dose of 5-HTP was found to cause diarrhoea and therefore was not used further. The 5-HTP-induced reduction in visceromotor threshold was not mimicked by the gastrointestinal prokinetic 5-HT$_4$ receptor agonist, cisapride, which had no significant effect on the distension pressures required to evoke a response (data not shown) at 100 μg kg^{-1}. This dose of cisapride is lower than that required to cause a 50% reduction of

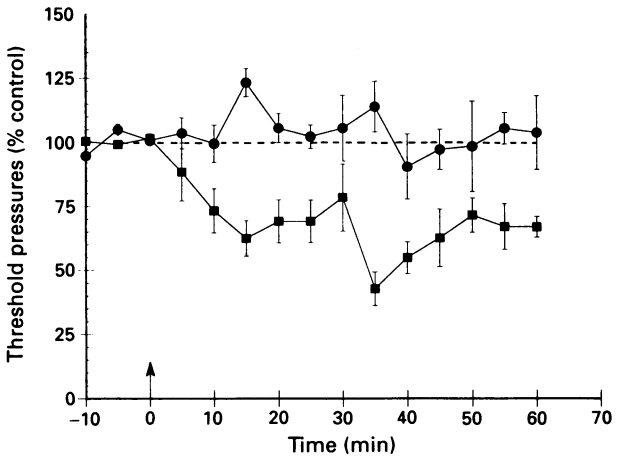

Figure 1 The effect of 5-hydroxytryptophan (■) at 10 mg kg^{-1} s.c. and saline vehicle (●) on threshold pressure values for visceromotor responses evoked by noxious colo-rectal distension, expressed as a % of control values. Points represent the mean ± s.e.mean of 11–13 animals.

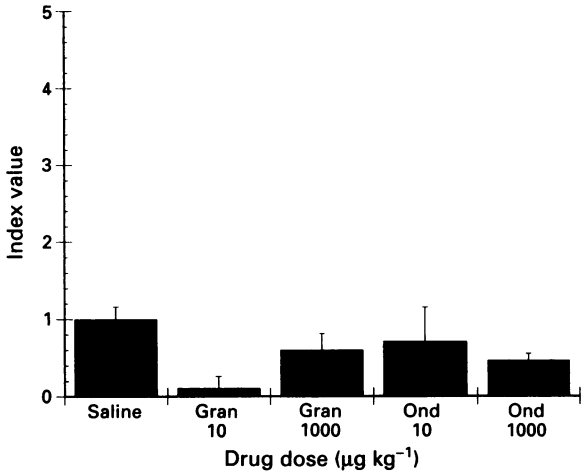

Figure 2 The effect of granisetron (Gran) and ondansetron (Ond) on visceromotor responses to noxious colo-rectal distension in normal rats, expressed as a function of the response to saline (index value of 1.0). Columns represent the mean ± s.e.mean of 6–7 animals.

the 5-HT-evoked Bezold-Jarisch reflex in rats (Dunbar *et al.* 1986).

Granisetron and ondansetron (both at 10 μg kg^{-1} and 1 mg kg^{-1}) in rats which were not pretreated with 5-HTP, did not affect the visceromotor threshold values (Figure 2). However, in rats predosed with 5-HTP (10 mg kg^{-1}), granisetron dose-dependently increased the visceromotor threshold values. The time course of this effect is demonstrated with a dose of 10 μg kg^{-1} in Figure 3. To compare the effects of different doses this effect of granisetron is expressed as an increase in the visceromotor threshold above the maximum percentage increase obtained in a separate groups of rats after dosing with saline (defined as 1.0, Table 1). A maximum 4.2 ± 0.6 fold increase in the pressures required to evoke a response was achieved for granisetron at 10 μg kg^{-1}. Further increases in the dose of granisetron resulted in a partial bell-shaped dose-effect curve, such that at doses up to 10 mg kg^{-1}, granisetron still reduced the hypersensitivity caused by 5-HTP, but to a lesser extent than that obtained with 10 μg kg^{-1} granisetron (Figure 4a). By comparison, ondansetron (10 μg kg^{-1}–10 mg kg^{-1}, Figure 4b) did not cause any increase in the visceromotor threshold values in the presence of 5-HTP. However, other 5-HT$_3$ receptor antagonists acted similarly to granisetron as demonstrated by zatosetron and

the trend shown by bemesetron. Both antagonists were also maximally effective at 10 μg kg^{-1} (Table 1). Table 1 also shows that quipazine at 100 μg kg^{-1} and renzapride at 10 μg kg^{-1} demonstrated good activity, whilst metoclopramide demonstrated weaker visceral analgesic properties. Tropisetron was considerably less potent than the most active antagonists with a tendency to increase at 1 mg kg^{-1}. BRL 46470A was without effect.

A further study was carried out with granisetron, to investigate whether endogenous opioids have a role to play in the action of this compound. Rats were pretreated with 5-HTP (10 mg kg^{-1}) and 5 min later with a dose of naloxone (5 mg kg^{-1}), which had no effect on responses to CRD. When a stable response was achieved, granisetron 10 μg kg^{-1} was administered and found to retain good visceral analgesic activity in the presence of naloxone with a 3.9 ± 0.8 ($n = 6$) fold increase in the drug/saline ratio compared to a 4.2 ± 0.6 fold increase in the absence of naloxone.

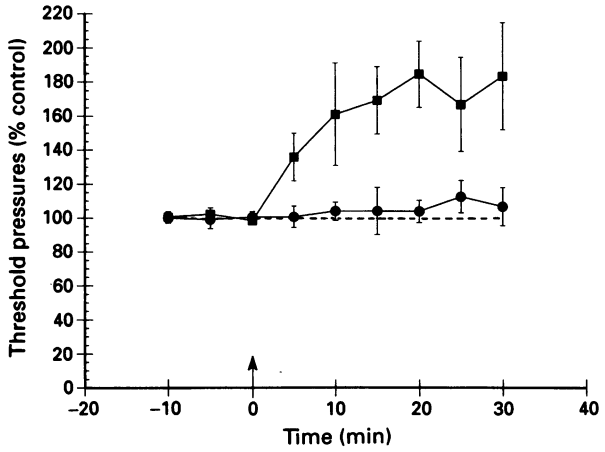

Figure 3 The effect of granisetron 10 μg kg^{-1}, s.c. (■) and saline vehicle (●) on threshold pressure values for visceromotor responses evoked by noxious colo-rectal distension in rats pretreated with 5-hydroxytryptophan, expressed as a % of control values. Points represent the mean ± s.e.mean of 11–16 animals.

Table 1 The effect of 5-HT$_3$ receptor antagonists on colorectal distension in the presence of 5-hydroxytryptophan (5-HTP)

Compound	*Dose* (μg kg^{-1} s.c.)	*Index*	P	n
Granisetron	0.1	1.6 (1.0)		6
	1	2.2 (0.4)	*	6
	10	4.2 (0.6)	***	16
	100	2.9 (0.7)	**	7
	1000	2.2 (0.4)		11
	10 000	2.0 (0.7)		8
Ondansetron	10	1.0 (0.2)		5
	100	0.9 (0.2)		5
	1000	0.4 (0.2)		6
	10 000	1.6 (0.5)		6
Zatosetron	1	2.7 (0.8)		5
	10	3.6 (0.4)	**	6
	100	2.7 (0.6)	*	6
Bemesetron	1	2.8 (0.7)		6
	10	3.7 (1.1)		6
	100	2.6 (0.8)		5
Quipazine	1	2.7 (0.9)		8
	10	3.1 (0.5)	*	6
	100	3.6 (0.8)	*	8
Renzapride	1	2.6 (0.9)		8
	10	3.8 (0.7)	**	8
Metoclopramide	1	1.9 (0.4)		6
	10	2.7 (0.4)	*	6
	100	2.2 (0.7)		7
Tropisetron	10	1.3 (0.3)		4
	100	1.8 (0.7)		5
	1000	2.0 (0.7)		8
	100 000	0.4 (0.8)		7
BRL 46470	1	0.5 (0.4)		5
	10	1.5 (0.3)		6
	100	0.02 (0.3)		6
	1000	0.6 (0.4)		6

Values are mean ± s.e.mean. Maximum post-dose increase in visceromotor threshold values indexed against saline (1.0). Student's t test significance: *$P<0.05$; **$P<0.01$ and ***$P<0.001$.

Discussion

Noxious visceral sensation can be consistently and reproducibly evoked by CRD (Ness & Gebhart, 1988). Analgesia in this model is represented as an increase in the threshold distension pressure above pre-dose stable control values, as demonstrated here by the analgesic, morphine. Although the possibility that morphine may have altered gastrointestinal tone cannot be excluded, distension of the balloon after dosing with 100 μg kg^{-1} caused cut-off levels to be reached prior to nociception, as anticipated with a strongly effective analgesic. Therefore, even with the limitation described, CRD is a useful model for determining the pharmacology of visceral nociceptive mechanisms.

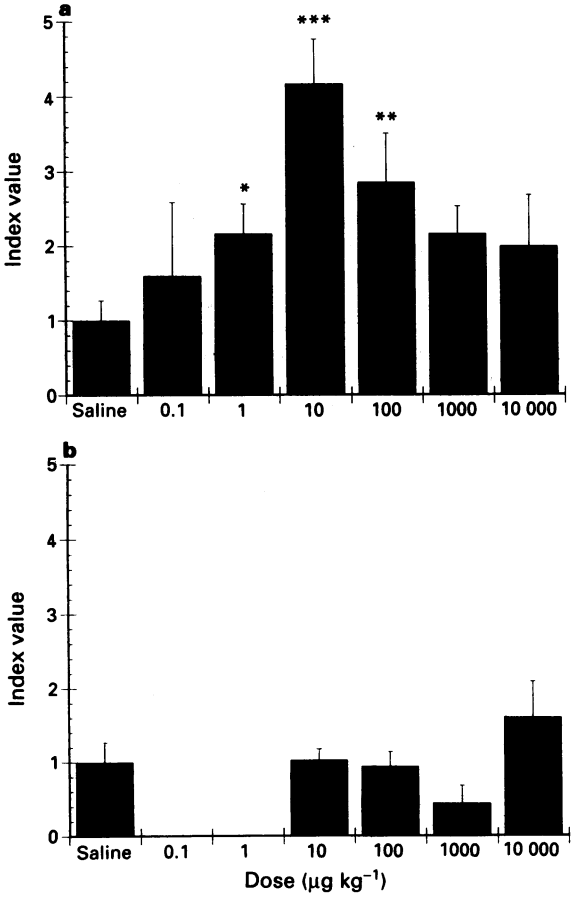

Figure 4 The effect of (a) granisetron and (b) ondansetron on responses to noxious colo-rectal distension in rats pretreated with 5-hydroxytryptophan, expressed as a function of the response to saline (index value of 1.0). Columns represent the mean ± s.e.mean of 5–16 animals; Student's t test significance: *$P<0.05$; **$P<0.01$; ***$P<0.001$.

The clinical study by Prior & Read (1993) demonstrated that the 5-HT$_3$ receptor antagonist, granisetron, increased the thresholds for the perception of sensations elicited by rectal distension in IBS patients with a hypersensitive bowel When it was found that the 5-HT$_3$ receptor antagonists, granisetron and ondansetron, had no effect on normal rats, which is in agreement with Danzebrink & Gebhart (1991), it was considered necessary to sensitize the rat colo-rectum in order to mimic the rectal hypersensitivity that typifies the IBS condition (see Mayer & Raybould, 1990). We found that rather than producing antinociceptive effects that may be expected by the activation of 5-HT-mediated, descending noxious inhibitory control pathways, 5-HTP lowered the visceromotor threshold. This hyperalgesic effect of 5-HTP was dose-dependent and clearly unrelated to the known propulsive motility properties of 5-HTP (Brittain & Collier, 1958) as the effect was not mimicked by the potent prokinetic and 5-HT$_4$ receptor agonist, cisapride. Despite the use of a very low dose of 5-HTP which did not induce diarrhoea, the fact that secretory mechanisms activated by the 5-HT precursor could still affect distension pressures in the colo-rectum cannot be totally dismissed and neither can the potential action of the antagonists at peripheral sensory nerve teminals. However, previous studies which demonstrated that intrathecal administration of granisetron caused complete blockade of blood pressure depressor, pseudoaffective reflexes, which occurred in response to colo-rectal distension in anaesthetized rats, support the hypothesis that at least some of the 5-HT effects may be outside the gut (unpublished observations).

When different 5-HT receptor antagonists were administered after sensitization with 5-HTP, variable effects were observed. Thus, certain structurally distinct antagonists appeared to raise the visceromotor threshold in an approximately equi-potent manner, thereby reducing the hypersensitivity induced by 5-HTP, whilst other antagonists had little or no effect. The former included granisetron, bemesetron and interestingly, metoclopramide. Tropisetron also tended to cause an increase in visceromotor thresholds but with reduced efficacy and at a relatively lower potency. In contrast, the structurally dissimilar compounds, BRL 46470A and ondansetron were found to be inactive. These differences in the ability of the selective 5-HT$_3$ receptor antagonists to produce antinociception in the rat appear to correlate with their clinical efficacy as analgesic drugs. Thus, in pilot studies granisetron has demonstrated its ability to raise the distension pressure required to elicit discomfort in IBS patients (Prior & Read, 1993). In preliminary clinical studies granisetron and bemesetron have been shown to be effective in the treatment of another visceral pain state, that of migraine (Loisy *et al.*, 1985; Couturier *et al.*, 1990; Rowat *et al.*, 1991). Tropisetron demonstrated only partial analgesic activity in migraine patients (Ferrari *et al.*, 1991). Similarly, metoclopramide has also been shown to have a clinical use as an analgesic in a variety of conditions (Hughes, 1977; Grauers *et al.*, 1982; Rosenblatt *et al.*, 1991; Coppola & Yealy, 1992; Kandler & Lisander, 1993). The least potent antagonist in the CRD model, ondansetron, was reported in studies on IBS patients to have variable effects in its ability to treat the associated pain to the extent that some patients complained of increased discomfort (Maxton *et al.*, 1991; Steadman *et al.*, 1990; 1992). A recent study similar to that of Prior & Read (1993) concluded that ondansetron did not alter the increased sensitivity or any index of colonic function, observed in IBS patients (Hammer *et al.*, 1993). Thus, these antagonists differ in their ability to inhibit nociception in man and this may be reflected in the present study.

The analgesic activity or lack of activity, of 5-HT$_3$ receptor antagonists described experimentally tends to correlate with clinical observations but fails to correlate pharmacologically with their ability to antagonize the 5-HT$_3$ receptor defined *in vivo* or *in vivo* in rats. Although, we cannot entirely rule out the possibility that these findings can be explained in terms of pharmacodynamics, against the rat Bezold-Jarisch reflex all antagonists, with the exception of metoclopramide and bemesetron, show good activity. Thus, i.v. ID_{50} values have been reported, ranging form 0.4 $\mu g\,kg^{-1}$ for tropisetron (Donatsch *et al.*, 1984) and 0.7 $\mu g\,kg^{-1}$ for granisetron (Fake *et al.*, 1987) to 3.6 $\mu g\,kg^{-1}$ for ondansetron (see Sanger, 1990) with bemesetron at 39 $\mu g\,kg^{-1}$ (Fozard, 1984) and metoclopramide at 377 $\mu g\,kg^{-1}$ (Fozard & Host, 1982). Furthermore, radioligand binding studies using the mammalian brain have demonstrated that these antagonists exhibit broadly similar K_i values except for metoclopramide (see review by Zifa & Fillion, 1992). Consequently, the findings presented here are suggestive of differences in the nature of the 5-HT$_3$ receptor involved in the mechanisms of visceral nociception. It may be significant that a recent study demonstrated that the release of 5-HT from enterochromaffin cells of guinea-pig isolated small intestine was inhibited by granisetron, bemesetron and tropisetron whilst ondansetron did not modify 5-HT release (Gebauer *et al.*, 1993) indicating potential differences in the actions of 5-HT$_3$ receptor antagonists.

The ability of granisetron to act as an analgesic in the presence of naloxone suggests that the 5-HT involvement in nociception is not modulated by opioid receptors, thereby eliminating one major pathway in nociceptive modulation. As such it can be suggested that this 5-HT$_3$-like receptor facilitates neurotransmission of nociceptive information rather than having a role in noxious inhibitory control.

In conclusion, 5-HT$_3$ receptor antagonists demonstrate a wide range of potency and efficacy for increasing threshold values to noxious colo-rectal distension in 5-HTP treated conscious rats. This model, which defines responses to colorectal hypersensitivity, may mimic conditions seen in the clinic and allow for the development of compounds which exploit potential differences between 5-HT$_3$ receptor antagonists, to address the dysfunction associated with visceral pain.

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