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Review paper

Emerging differences between 5-HT_3 receptor antagonists

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A brief review is presented of some recently described 5-HT_3 receptor antagonists. These antagonists are primarily targeted for use as anti-emetics. However, evidence is emerging that there are differences in their basic pharmacology. This evidence is reviewed in terms of the selectivity of the antagonists in binding studies and also of their efficacy in emesis and gastric emptying. The possibility that these differences may translate into meaningful clinical differences between the available 5-HT_3 receptor antagonists in their use as anti-emetics is also discussed.

Key words: Emesis, gastric motility, granisetron, 5-HT_3, ondansetron.

Introduction

It was recognized as long ago as 1970 that the substituted benzamide, metoclopramide, could antagonize the action of 5-hydroxytryptamine (5-HT) receptors at neuronal receptor sites in the gut.[1] The ability of high doses of metoclopramide to block chemotherapy-induced vomiting in man[2] was linked by Miner and Sanger to the activity of metoclopramide at the 5-HT_3 (or M) receptor site and led to the demonstration that a selective 5-HT_3 receptor antagonist could block cisplatin-induced vomiting in the ferret.[3] 5-HT_3 receptors, believed to be situated both centrally and peripherally in the gastrointestinal system, have become of interest for their role in the regulation of the emetic response to cytotoxic drugs and whole body X-irradiation, and also in the regulation of gastrointestinal motility.

Development of the first selective 5-HT_3 receptor antagonists began with MDL 72222[4] and tropisetron[5] and since then other 5-HT_3 receptor antagonists have been synthesized: renzapride,[6] granisetron,[7] ondansetron[8] and zacopride.[9] Studies of their prokinetic effects and pharmacodynamic properties have made it clear that not all of these compounds are equally specific and indeed the existence of a fourth 5-HT receptor subtype is now being proposed.[10]

Emesis

5-HT_3 receptors appear to be involved in the emetic mechanism evoked by cytotoxic drugs or radiotherapy. The hypothesis was originally proposed by Miner and Sanger[3] who showed that MDL 72222 blocked cisplatin-induced emesis in the ferret. It has been suggested that the 5-HT_3 receptors are located on visceral afferent nerve terminals within the abdomen, and on a non-abdominal site, possibly located within the area postrema which contains the emetic chemoreceptor trigger zone.[11] Agents such as cisplatin may disrupt cells containing 5-HT in the gastrointestinal tract, allowing receptor stimulation.[12]

Tropisetron,[13] granisetron,[11] ondansetron[14] and renzapride,[15] administered intravenously, orally or intraperitoneally, have all been shown to inhibit cisplatin-induced emesis in the ferret. In addition, ondansetron, injected directly into the area postrema of the ferret after the first emetic episode, inhibited further emesis at a lower dose than was required by peripheral administration, although the protective effect had a relatively long onset and short duration of action.[16]

Zacopride has been shown to be effective in blocking further vomiting in cats, when given intracerebroventricularly (i.c.v.), after the first

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emetic episode following administration of cisplatin.[17] In contrast, granisetron (0.5 mg/kg i.v.) has a rapid onset of action (within 5–20 s) when given as intervention against cisplatin-induced emesis in the ferret,[11] but is ineffective in the dog when injected i.c.v. (0.05–0.2 mg) 5 min after cisplatin administration.[18] Such differences in anti-emetic effectiveness, particularly those between granisetron and ondansetron, may be due to action at different 5-HT_3 receptor sites, i.e. central sites, or peripheral sites located in the gut. A recent study showed that granisetron was a more potent inhibitor of cisplatin-induced emesis in the ferret when given orally than when administered intravenously. The reverse was true for ondansetron.[19]

In man, tropisetron,[20] granisetron[21] and ondansetron[22] are all potent inhibitors of nausea and vomiting induced by cytotoxic drugs. For tropisetron, no dose–response relationship was observed at single doses of 5, 10 and 20 mg/m^2 i.v.[23] and studies with granisetron[24] showed efficacy to be similar following single doses of 40 and 160 μg/kg i.v. A dose-ranging study involving ondansetron (0.01–0.48 mg/kg i.v. × 3) was also unable to demonstrate a clear dose–response relationship, and there appeared to be a reduction in the anti-emetic efficacy at the highest dose tested.[25]

Pharmacodynamics and receptor binding

In the last few years a range of studies has been carried out to describe the relative potency and activity of the different 5-HT_3 receptor antagonists.

An established model for 5-HT_3 receptor antagonist activity is the Bezold–Jarisch reflex—5-HT-evoked bradycardia in the anesthetized rat. Cohen *et al.* have used this model to test relative potency of three 5-HT_3 receptor antagonists.[26] After intravenous administration their relative potency as inhibitors of the Bezold–Jarisch reflex was zacopride > tropisetron = ondansetron. This rank order was similar after oral administration, although, in this case, tropisetron was about twice as potent as ondansetron. Not only was zacopride the most potent of the compounds assessed, it also had the longest duration of action after oral administration. Maximal inhibition of 5-HT-evoked bradycardia was maintained for 6 h, whereas inhibition was minimal after 3 and 6 h with ondansetron and tropisetron, respectively. After intravenous administration, no inhibition of the Bezold–Jarisch reflex was obtained 15 min after dosing with ondansetron.

This order of potency in the Bezold–Jarisch reflex has been confirmed in our own laboratories where zacopride > granisetron > tropisetron > ondansetron. A similar order was found against contractions induced by 5-HT and 2-methyl-5-HT in guinea-pig ileum: granisetron > zacopride > tropisetron > ondansetron (Table 1).

In addition to their location in peripheral tissues, 5-HT_3 binding sites have been identified in central nervous system tissue. Kilpatrick *et al.*[27] reported the presence of 5-HT_3 receptors in rat brain tissue using radiolabeled GR65630, a ring-opened analog of ondansetron. Their results demonstrated that GR65630 and ondansetron were also bound to a second, low-affinity site, unrelated to the 5-HT_3 receptors. Tropisetron and granisetron had no affinity for this site. These results were confirmed by Van Wijngaarden *et al.*[28] who reported that this second site accounted for about 20% of total binding in the case of GR65630 and ondansetron. They concluded that only tropisetron and granisetron merited a description as highly selective 5-HT_3 antagonists (ratios >1000), and that ondansetron lacked this distinction (ratio <1000).

Similar experiments have used either radiolabeled zacopride[29] or granisetron[30] to identify 5-HT_3 recognition sites in rat cortical tissue, and radiolabeled tropisetron in mouse neuroblastoma–glioma[31] cells. Each ligand was bound to a single population of sites and was displaced by known 5-HT_3 receptor antagonists whose order of potency was, generally: zacopride > tropisetron (or granisetron) > granisetron (or tropisetron) > ondansetron. However, use of [^{3}H]zacopride in rabbit ileum muscularis membranes revealed two

Table 1. The 5-HT_3 receptor antagonism of granisetron, ondansetron, tropisetron and zacopride against the 5-HT-induced Bezold–Jarisch reflex in the anesthetized rat, and 5-HT- and 2-methyl-5-HT-induced contractions in the isolated guinea-pig ileum

	ID_{50}[a] (*n*) μg/kg i.v.	PA_2[b] 5-HT	PA_2[b] 2-Me-5-HT
Granisetron	0.38 ± 0.10 (10)	7.92 ± 0.18	8.53 ± 0.10
Zacopride	0.34 ± 0.06 (6)	7.80 ± 0.19	—
Tropisetron	1.50 ± 0.39 (7)	7.57 ± 0.22	8.11 ± 0.29
Ondansetron	4.14 ± 0.86 (7)	7.10 ± 0.23	7.99 ± 0.21

Results are expressed as mean ± SEM.
[a] In the Bezold–Jarisch reflex.
[b] In the guinea-pig ileum.
(*n*) No. of animals; *n* = 6 for all experiments in the ileum.

such binding sites—a salt-insensitive, 5-HT$_3$-specific site and a salt-sensitive, currently unidentified one.[32] Van Wijngaarden[28] has pointed out that the latter may correspond to the 5-HT$_4$ receptor recently proposed by Dumuis *et al.*[33]

Gastrointestinal motility

Metoclopramide is believed to stimulate gut motility and accelerate gastric emptying by increasing release of acetylcholine from cholinergic nerve endings in the gut, possibly via antagonism of an enteric 5-HT receptor.[34] This has led to investigation of the prokinetic effects of selective 5-HT$_3$ receptor antagonists. Pooling the results of several studies, however, leads to a somewhat confusing picture as the relative potency and efficacy of the 5-HT$_3$ receptor antagonists varies across the range of different models used.

In some studies, ondansetron and renzapride appeared to be more effective than either tropisetron or granisetron. For example, both ondansetron and renzapride[35] produced enhancement of electrically evoked contractions of rat stomach strips, whereas neither tropisetron[35] nor granisetron[35,36] had any effect (although tropisetron did increase contractions in guinea-pig stomach strips).[37] Renzapride also enhanced electrically evoked contractions in the guinea-pig ileum; tropisetron[34] and granisetron[36] were ineffective.

In vivo results reflect some of the differences demonstrated in these *in vitro* experiments. Ondansetron has been shown to increase spontaneous activity in the rat stomach and suppress contractions induced by 5-HT.[38,39] Granisetron, however, did not consistently affect rat gastric motility.[7] Other studies have shown that ondansetron increased the response to vagal stimulation in the anesthetized rat stomach at intraarterial doses of 5×10^{-14} to 5×10^{-13} M.[38] In the anesthetized rat, it was found that both granisetron (100–1000 μg/kg i.v.) and ondansetron (10–1000 μg/kg i.v.) increased relaxations induced in the stomach by vagal stimulation (Table 2), ondansetron being both more potent and more effective.

Buchheit *et al.*[35] ranked a number of 5-HT$_3$ receptor antagonists in order of potency as accelerators of gastric emptying in the rat. Emptying of a solid meal was increased in the order ondansetron > renzapride > tropisetron = granisetron. Ondansetron (0.1 mg/kg i.v.) has been shown to facilitate charcoal transit in the mouse, although higher doses (1–4 mg/kg i.v.) were without effect.[39] Granisetron (0.003–0.3 mg/kg i.p.) has no effect on meal transit in the rat (Table 3).

Other studies, however, have shown tropisetron and granisetron to be more effective than ondansetron and renzapride. Buchheit and coworkers[35] also measured liquid meal emptying in the rat and found a rank order of potency of tropisetron = granisetron > ondansetron = renzapride.

In a model of visceral pain, both granisetron and tropisetron reduced the fall in blood pressure induced by noxious duodenal distension while ondansetron had no effect on the distension-evoked response.[40] *In vitro* studies of fecal pellet transit showed that while transit was slowed with granisetron and tropisetron, ondansetron was without effect.[41] In the rat, however, ondansetron was able to inhibit the increase in defecation frequency induced by 5-HT.[42]

In a third group of studies, tropisetron, granisetron and ondansetron have been shown to behave in a similar manner. Gastric emptying in the guinea-pig has been measured after both central and peripheral administration. Tropisetron, when injected into the hypothalamus, increased solid gastric

Table 2. The effect of granisetron (10–1000 μg/kg i.v.) and ondansetron (10–1000 μg/kg i.v.) on the relaxation induced by vagal stimulation (10 V, 0.1 ms; 2 Hz for 10 s) in the anesthetized rat stomach

	Dose (μg/kg i.v.)		
	10 (*n*)	100 (*n*)	1000 (*n*)
Granisetron	102 ± 6 (8)	143 ± 17* (8)	170 ± 24* (9)
Ondansetron	156 ± 19* (7)	168 ± 20** (9)	189 ± 22* (5)

(*n*) No. of animals. Results were calculated as a percentage of the control response and expressed as mean ± SEM. Means were compared using Student's *t*-test and results which were significantly different from control values were identified.
* $p \leq 0.05$; ** $p \leq 0.01$.

Table 3. The effect of granisetron (0.003–0.3 mg/kg s.c.) on charcoal meal transit in the rat

	Granisetron (mg/kg s.c.)					
	Control (*n*)	0.003 (*n*)	0.01 (*n*)	0.03 (*n*)	0.1 (*n*)	0.3 (*n*)
Transit (%)	55.3 ± 1.5 (12)	58.0 ± 1.2 (6)	52.5 ± 2.4 (6)	59.7 ± 11.5 (12)	50.2 ± 2.6 (6)	48.8 ± 3.8 (6)

(*n*) No. of animals. The dose of granisetron was given 15 min before administration of the charcoal meal, and transit was measured 15 min after the meal. The distance travelled by the meal down the small intestine was expressed as a percentage of the total length of the intestine, to give a measure of transit. Results were expressed as mean ± SEM and compared using Student's unpaired *t*-test. No significant differences in mean values were found between dose groups.

emptying with an activity about equal to that of metoclopramide.[43] When administered peripherally, tropisetron was shown to be 10–50 times more potent than metoclopramide,[37] and ondansetron, in similar experiments, about 200 times more potent,[44] reflecting the order of potency seen in the rat.

In man, neither granisetron[45] nor ondansetron[46] were found to affect gastric emptying time. Results with tropisetron have been variable; some authors have observed modest increases in solid emptying[47] whereas others have reported no increases following ingestion of a semi-solid (fat) meal, and even, at higher doses, a decrease.[48] Granisetron, ondansetron and tropisetron have all been reported to cause constipation in volunteer studies in man. Ondansetron has been shown to slow colonic transit[46,49] and tropisetron to cause an increase in colonic motor activity.[50]

Thus, it would seem that different models are able to highlight differences in the mode of action of some of the 5-HT_3 antagonists. The reason for these differences is presently unclear, but may reflect activity at different sites, i.e. central or peripheral, the presence of 5-HT_3 receptor subtypes, or activity of one or more of the antagonists at a receptor other than the 5-HT_3.

Discussion

It is currently believed that in the normal gastrointestinal system, neuronal 5-HT regulates the motor response. This is mediated by 5-HT_3 receptors although the activity and affinity of different 5-HT_3 receptor antagonists appears to be tissue- and/or species-dependent. Ondansetron and renzapride have similar prokinetic effects. They both enhance electrically evoked contractions in rat stomach, as does renzapride in guinea-pig ileum and human stomach. Ondansetron increases gastric motility in the rat, and both compounds increase solid gastric emptying more potently than do tropisetron and granisetron. Neither tropisetron nor granisetron enhance electrically evoked contractions in the rat stomach. Granisetron does not increase rat gastric motility and tropisetron is less active than ondansetron in increasing bead emptying in the guinea-pig.

It is unclear whether these differences are due to the existence of 5-HT_3 receptor subtypes, or whether some of these compounds act at a separate 5-HT receptor site, i.e. a 5-HT_4 receptor. Support for this latter view comes from binding studies of 5-HT_3 receptor antagonists. Both ondansetron and its ring-opened analog, GR65630, bind to a second site in rat brain tissue and zacopride binds to two sites in rabbit ileum muscularis membrane. Dumuis *et al.* has recently proposed that it is appropriate to identify a fourth 5-HT binding site (5-HT_4) where renzapride and metoclopramide are active. Tropisetron, it is thought, acts as an antagonist at this site.[51] Available evidence now suggests that the substituted benzamides—metoclopramide, zacopride, renzapride and cisapride—may partly owe their prokinetic effects to agonist activity at this 5-HT_4 receptor.[12] Whether this receptor is the same as the additional binding site identified with GR65630 and zacopride remains to be clarified.

In summary, the anti-emetic 5-HT_3 receptor antagonists can be roughly split into two groups on the basis of their prokinetic activity; those which are renzapride-like, and those which are granisetron-like. From the current evidence, it would appear that ondansetron may fall into the renzapride group and, in general, tropisetron behaves in a similar way to granisetron, although it would appear to have additional properties. Further

clinical work is required to examine the impact of this on the clinical use of these compounds as anti-emetics, but a loss of selectivity may lead to a loss of efficacy at higher doses.

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