VISCERAL PERCEPTION

Serotonergic modulation of visceral sensation: upper gastrointestinal tract

J Tack, G Sarnelli

Gut 2002;51(Suppl 1):i77-i80

Agents that modify serotonergic function have therapeutic potential for the treatment of visceral hypersensitivity, either through a direct effect on perception or through modulation of visceral tone or motility. Administration of selective serotonin reuptake inhibitors reduces oesophageal sensitivity to distension but not gastric sensitivity to distension. 5-HT ligands may also influence gastric mechanosensitivity by altering tone. Although the exact role of 5-HT receptors in the control of gastrointestinal functions remains unknown, 5-HT is generally considered to be the main candidate involved in the modulation of motor and sensory function from the gastrointestinal tract. Hence serotonergic modulation of upper gut sensitivity appears to be promising for the development of novel approaches to the treatment of functional disorders of the upper gastrointestinal tract.

SUMMARY

Agents that modify serotonergic function have therapeutic potential for the treatment of visceral hypersensitivity, either through a direct effect on perception or through modulation of visceral tone or motility. Administration of selective serotonin reuptake inhibitors (SSRIs) reduces oesophageal sensitivity to distension but not gastric sensitivity to distension. Administration of amitriptyline to patients with functional dyspepsia has no effect on sensitivity to gastric distension but may provide symptomatic benefit. The 5-HT₃ antagonist ondansetron partly reverses sensitisation to gastric distension during duodenal lipid infusion. 5-HT ligands may also influence gastric mechanosensitivity by altering tone. Cisapride, a 5-HT₄ agonist/weak 5-HT₃ antagonist induces a small degree of gastric contraction in the fasting state but postprandially it markedly enhances gastric accommodation. Similarly, the SSRI paroxetine enhances relaxation in response to a liquid meal and may provide symptomatic benefit for patients with impaired gastric accommodation. The 5-HT_{1D} receptor agonist sumatriptan activates intrinsic inhibitory neurones in the stomach. The resulting gastric relaxation has been shown to reduce postprandial symptoms in patients with functional dyspepsia caused by hypersensitivity. Buspirone, a 5-HT_{1A} agonist, reduces cholinergic tone to the stomach, thereby increasing the threshold for discomfort and reducing the severity of dyspeptic symptoms.

See end of article for authors' affiliations

Correspondence to:
Dr J Tack, Department of
Internal Medicine, Division
of Gastroenterology,
University Hospital
Gasthuisberg, Herestraat
49, B-3000 Leuven,
Belgium;
jan.tack@med.kuleuven.ac.be

INTRODUCTION

Serotonin and the gastrointestinal tract

Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter in the central nervous system (CNS). The presence of 5-HT in the gastrointestinal tract has been demonstrated immunohistochemically in enterochromaffin (EC) cells and also in enteric neurones.¹⁻³ Release of 5-HT and other paracrine messengers from EC cells act as chemical and mechanical transducers for the initiation of local reflexes (for example, peristalsis) and for activation of afferent projections to the CNS.⁴⁻⁶

Accumulating evidence supports the hypothesis that 5-HT is a neurotransmitter in the enteric nervous system (ENS).⁴⁻⁵ However, due to the presence of multiple 5-HT receptor subtypes, and the lack of suitable ligands that can be safely used *in vivo*, the physiological role of neuronal 5-HT in the gastrointestinal tract remains unclear.⁴⁻⁵⁻⁷

Visceral sensation is modulated at different levels of the brain-gut axis. The neuroanatomical pathways involved in this process have been reviewed extensively.⁶⁻⁸⁻¹⁰ The gastrointestinal tract can respond to different sensory modalities, including chemo-, thermo-, and mechanosensitivity. Of these, only visceral mechanosensitivity has been studied in depth. Under normal circumstances, most of the visceral input to the CNS is not perceived consciously. Patients with functional bowel disease are thought to perceive visceral stimuli in an abnormal manner¹⁰ but it is not clear at what level this originates. An altered threshold of visceral mechanoreceptor sensitivity, altered modulation in the conduction of sensorial input, or a lowered pain threshold at a central level have all been suggested.⁶⁻⁸⁻¹⁰

The role of 5-HT in visceral perception requires further investigation. Descending serotonergic systems present in supraspinal and spinal pathways are thought to be involved in the modulation of antinociception, which suggests that 5-HT ligands may have the potential to alter visceral perception.¹¹⁻¹³ Although the exact role of 5-HT receptors in the control of gastrointestinal functions remains unknown, 5-HT is generally considered to be the main candidate involved in the modulation of motor and sensory function from the gastrointestinal tract,⁴⁻⁸⁻⁹ and consequently 5-HT receptor ligands are being used, or are under investigation for use, in the treatment of different functional gastrointestinal disorders.

Abbreviations: CNS, central nervous system; EC, enterochromaffin cells; ENS, enteric nervous system; SSRIs, selective serotonergic reuptake inhibitors; 5-HT, serotonin.

Figure 1 Overview of 5-HT receptors expressed on myenteric neurones in the stomach, based on studies in guinea pigs. ACh, acetylcholine; Sub P, substance P; NO, nitric oxide; VIP, vasoactive intestinal peptide.

5-HT RECEPTORS AND 5-HT RECEPTOR LIGANDS

Several 5-HT receptor subtypes have been identified in the gastrointestinal tract. These are located in nerves or on smooth muscle cells where they mediate a number of different actions (fig 1).⁷⁻⁸ Although a growing number of 5-HT receptor agonists and antagonists are available, only a limited number of selective ligands are suitable for human studies (table 1).

Enteric neurones resemble central serotonergic neurones in terms of their response to 5-HT reuptake inhibitors.¹⁴⁻¹⁵ SSRIs prolong the availability of physiologically released 5-HT and thereby enhance the effects of 5-HT released synaptically from neurones located centrally as well as those originating at the level of the ENS (fig 2).¹⁴⁻¹⁵ These agents have to be used to study involvement of 5-HT in gastrointestinal sensorimotor function in humans.

Non-SSRIs such as the tricyclic antidepressants have received a relatively high level of attention whereas the effects of SSRIs on gastrointestinal function and their role in the treatment of functional gastrointestinal disorders remains largely unexplored.

SEROTONERGIC MODULATION OF OESOPHAGEAL SENSITIVITY

Conflicting results have been reported concerning the ability of 5-HT to modify oesophageal sensitivity. According to one study, administration of the tricyclic antidepressant amitriptyline, a non-SSRI, failed to alter thresholds for perception, discomfort, and pain induced by oesophageal balloon distension.¹⁶ However, in another study, the tricyclic antidepressant imipramine reduced the pain threshold, but not the perception threshold, during balloon distension in healthy volunteers but the difference was small.¹⁷ Recently, we demonstrated that administration of the SSRI citalopram significantly lowered mechano- and chemosensitivity in healthy subjects.¹⁸ The action of citalopram occurred without alteration of basal oesophageal motility. Although this finding supports the involvement of 5-HT in the modulation of oesophageal sensitivity, it does not provide information about whether a central or peripheral mechanism of action is involved.

Motility abnormalities and hypersensitivity to acid, cholinergic agents, and intraluminal distension stimuli are pathophysiological abnormalities found in patients with non-cardiac chest pain.¹⁹⁻²⁰ The results of a relatively small study

Table 1 Overview of 5-HT receptors and their ligands

Subtype	Selective agonist	Selective antagonist	Non-selective agonist	Non-selective antagonist
1A	8-OH-DPAT	WAY 100365	<i>Buspirone</i>	
1B	<i>Sumatriptan</i>	GR 55562		
1D	<i>Sumatriptan</i>	BRL 15572		
1F	LY 334370			
2A	α -Me-5-HT	<i>Ketanserin</i> MDL 100907		<i>Mianserin</i>
2B	α -Me-5-HT BV 723C86	SB 200646 SB 204741		<i>Cyproheptadine</i>
2C	α -Me-5-HT	Mesulergine SB 242084 RS 102221		<i>Cyproheptadine</i>
3	SR 57227 Chlorophenyl-biguanide	<i>Odansetron</i> <i>Granisetron</i> <i>Alosetron</i> <i>Tropisetron</i>		
4	BIM U8 RS 67506 ML 10302 <i>Tegaserod</i> <i>Prucalopride</i>	GR 113808 SB 204070 RS 100235	<i>Cisapride</i> <i>Renzapride</i>	

Those suitable for use in humans are italicised.

Figure 2 Rationale for the use of selective serotonergic reuptake inhibitors (SSRIs) and the role of 5-HT in gastrointestinal sensorimotor function.

($n=19$) showed that imipramine improved symptoms in these patients but chemo- or mechanosensitivity of the oesophagus was not investigated.²¹ However, the authors suggested that the improvement might have been associated with a 5-HT mediated visceral analgesic effect. Preliminary data indicate that ondansetron increases oesophageal thresholds to distension in patients with non-cardiac chest pain suggesting that the 5-HT₃ receptor may play a role in this response.²² Further studies are required to confirm this finding.

SEROTONERGIC MODULATION OF GASTRIC SENSITIVITY

Influence on perception to gastric distension

SSRIs do not appear to affect sensitivity to gastric distension.²³ Likewise, preliminary studies using the non-selective antagonists of 5-HT_{2A} and 5-HT_{2B} receptor subtypes cyproheptadine and mianserin were also unable to affect the mechanical induced gastric sensation in humans (unpublished observations). In a small group of patients, the non-selective SSRI amitriptyline provided symptomatic benefit in the absence of a change in gastric sensitivity to distention.²⁴

Studies in animals suggest that 5-HT₃ receptors are putative excitatory mediators in visceral sensory pathways, and thus 5-HT₃ antagonists may reduce the level of perception to visceral distension.²⁵ However, in human studies this effect has only been observed in the lower part of the gastrointestinal tract.²⁶ The selective 5-HT₃ antagonists alosetron and ondansetron do not appear to have any significant effects on sensitivity to gastric distension.^{27–28} These observations suggest that gastric mechanosensitivity is not mediated through release of 5-HT in humans. However, this does not preclude an action of 5-HT ligands on sensitivity to mechanical distension.

Influence on fasting and postprandial gastric tone

The main determinant of gastric mechanosensitivity is gastric tone. A subset of patients with functional dyspepsia have been shown to have insufficient accommodation (decrease in gastric tone) after a meal.^{29–30} It is possible therefore that serotonergic ligands, which influence fasting and postprandial gastric tone, may also affect sensitivity to gastric distension.¹⁰

Short pretreatment with the SSRI paroxetine has been shown to enhance gastric accommodation to a meal in healthy volunteers in the absence of any effect on fasting gastric compliance.²³ These observations suggest that 5-HT release is involved in the control of the accommodation reflex and therefore in the modulation of visceral sensation during the postprandial state. In support of this hypothesis, 5-HT_{1A}, 5-HT_{1P}, 5-HT₂, and 5-HT₄ receptors have all been identified on myenteric neurones in the guinea pig stomach.³¹

Pretreatment with 5-HT₃ receptor antagonists was found to have no influence on fasting or postprandial gastric tone in healthy volunteers.^{27–28} However, activation of 5-HT₄ receptors,

believed to be located presynaptically on nerve terminals of enteric cholinergic interneurons and motor neurones (fig 1), has been shown to enhance the release of acetylcholine from cholinergic nerve endings, resulting in increased contractility.^{32–33}

Prokinetic benzamides, such as cisapride, act as 5-HT₄ receptor agonists. Their gastrokinetic properties are thought to originate from their ability to stimulate 5-HT₄ receptors on cholinergic nerve terminals.^{33–34} In humans, pretreatment with cisapride has been shown to shift gastric volume-pressure relationships towards higher pressures for the same distending volume. This effect was associated with lowered discomfort thresholds during gastric distension. Surprisingly, cisapride has also been shown to enhance gastric accommodation to a meal.³⁵

The effect of 5-HT in a subset of myenteric neurones is known to evoke a slow depolarising response. This effect is mediated by the so-called 5-HT_{1P} receptors which are predominantly located on inhibitory motor neurones of the gastric myenteric plexus (fig 1).^{31–36} Recent studies have identified sumatriptan as a 5-HT_{1P} receptor agonist which interacts with nitrergic myenteric neurones in the guinea pig stomach and which induces gastric relaxation in cats and humans.^{37–39} In acute studies, sumatriptan has been shown to enhance the intragastric volumes needed to induce perception and discomfort in fasted healthy volunteers,³⁸ and to normalise meal induced relaxation and improve symptoms of early satiety in patients with impaired postprandial accommodation.³⁰

A subset of patients with functional dyspepsia have hypersensitivity to gastric distension accompanied by more prevalent symptoms of pain, belching, and weight loss.⁴⁰ Sumatriptan was found to decrease sensitivity to distension in patients with hypersensitivity to gastric distension. It also improved symptoms that followed eating a standardised meal, possibly by decreasing the level of activation of tension mechanoreceptors.⁴¹

The non-selective 5-HT_{1A} receptor agonist buspirone is thought to decrease gastric tone and increase the distension induced volume thresholds in healthy volunteers, thereby mimicking some of the effects of sumatriptan.⁴² In a placebo controlled, double blind, randomised, crossover study, buspirone was shown to be superior to placebo at improving gastric accommodation in patients with functional dyspepsia. Based on these findings, SSRIs, 5-HT₄ receptor agonists, 5-HT_{1P} receptor agonists, and 5-HT_{1A} receptor agonists all appear to have beneficial effects in patients with functional dyspepsia and impaired accommodation.⁴³ The 5-HT_{1P} and 5-HT_{1A} receptor agonists may have additional therapeutic potential for the treatment of gastric visceral hypersensitivity. The effect of these agents on visceral sensitivity appears to be associated with a change in gastric tone.

SEROTONERGIC MODULATION OF DUODENAL SENSITIVITY

Upper gastrointestinal viscerovisceral reflexes are predominantly mediated through vagal afferents and triggered physiologically by intestinal mechanical stimuli and by the presence of duodenal nutrients.^{44–45} Several observations suggest the involvement of 5-HT in the control of duodeno-gastric reflexes.

In animals, low intensity non-painful duodenal distension inhibits gastric motility. This response is abolished by low doses of granisetron administered peripherally but not centrally, suggesting a peripheral site of action for this 5-HT₃ antagonist.⁴⁶ In humans, ondansetron reduces the sensation of nausea provoked by the combined stimuli of intraduodenal lipid infusion and gastric distension.⁴⁷ As the drug does not alter gastric tone or sensitivity, it probably acts at duodenal vagal afferents.^{27–28}

A recent study demonstrated reduction in dyspepsia symptoms in patients treated with the 5-HT₃ receptor antagonist alosetron.⁴⁸

CONCLUSION

Serotonergic modulation of upper gut sensitivity appears promising for the development of novel approaches to the treatment of functional disorders of the upper gastrointestinal tract.

Authors' affiliations

J Tack, G Sarnelli, Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium

REFERENCES

- 1 Erspamer V. Occurrence of indolealkylamines in nature. In: Erspamer V, ed. *Handbook of experimental pharmacology*. vol 19: 5-Hydroxytryptamine and related indolealkylamines. New York: Springer Verlag, 1966:132–81.
- 2 Mawe GM, Schemann M, Wood JD, et al. Immunocytochemical analysis of potential neurotransmitters present in the myenteric plexus and muscular layers of the corpus of the guinea-pig stomach. *Anat Rec* 1989;**224**:431–42.
- 3 Vanden Berghe P, Coulie B, Tack J, et al. Neurochemical coding of myenteric neurons in the guinea pig antrum. *Cell Tissue Res* 1999;**297**:81–90.
- 4 Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther* 1999;**13**(suppl 2):15–30.
- 5 Gershon MD. The enteric nervous system *Annu Rev Neurosci* 1981;**4**:227–72.
- 6 Mayer EA, Gebhart FG. Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology* 1994;**107**:271–93.
- 7 Hoyer D, Clarke DE, Fozard JR, et al. International union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev* 1994;**46**:157–203.
- 8 Sanger GJ. 5-Hydroxytryptamine and functional bowel disorders. *Neurogastroenterol Motil* 1996;**8**:319–31.
- 9 Cervero F. Visceral hyperalgesia revisited. *Lancet* 2000;**356**:1127–8.
- 10 Camilleri M, Coulie B, Tack J. Visceral hypersensitivity: facts, speculations and challenges. *Gut* 2001;**48**:125–31.
- 11 Sawynok J, Reid A. Interactions of descending serotonergic systems with other neurotransmitters in the modulation of nociception. *Behav Brain Res* 1996;**73**:63–8.
- 12 Bueno L, Fioramonti J, Delvaux M, et al. Mediators and pharmacology of visceral sensitivity: from basic to clinical investigations. *Gastroenterology* 1997;**112**:1714–43.
- 13 Yaksh TL, Wilson PR. Spinal serotonin terminal system mediates antinociception. *J Pharmacol Exp Ther* 1979;**208**:446–53.
- 14 Gershon MD, Jonakait GM. Uptake and release of 5-hydroxytryptamine by enteric 5-hydroxytryptaminergic neurones: effects of fluoxetine (Lilly 110140) and chlorimipramine. *Br J Pharmacol* 1979;**66**:7–9.
- 15 Wade PR, Chen J, Jaffe B, et al. Localization and function of a 5-HT transporter in crypt epithelia of the gastrointestinal tract. *J Neurosci* 1996;**16**:2352–64.
- 16 Gorelick AB, Koshy SS, Hooper FG, et al. Differential effects of amitriptyline on perception of somatic and visceral stimulation in healthy humans. *Am J Physiol* 1998;**275**:G460–6.
- 17 Peghini PL, Katz PO, Castell DO. Imipramine decreases oesophageal pain perception in human male volunteers. *Gut* 1998;**42**:807–13.
- 18 Broekaert D, Vos R, Sifrim D, et al. Influence of citalopram, a selective 5-hydroxytryptamine reuptake inhibitor, on esophageal sensitivity and motility in man. *Gastroenterology* 2000;**120**:A629.
- 19 Demedts I, Tack J. Chest pain of esophageal origin. *Curr Opin Gastroenterol* 1998;**14**:340–4.
- 20 Tack J, Janssens J. The esophagus and noncardiac chest pain. In: Castell DO, Richter J, eds. *The esophagus*. Lippincott-Raven, 1998:581–94.
- 21 Cannon RO III, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994;**330**:1411–17.
- 22 Stark M Jr, Maher K, Gupta P. Visceral afferent blockade with ondansetron increases nociceptive thresholds in patients with non cardiac chest pain. *Am J Gastroenterol* 1991;**18**:A129.
- 23 Tack J, Schnackcrs D, Coulie B, et al. 5-HT is involved in the gastric accommodation reflex in man [abstract]. *Neurogastroenterology and motility* 1998;**10**:475.
- 24 Mertz H, Fass R, Kodner A, et al. Effect of amitriptyline on symptoms, sleep, and visceral perception in patients with functional dyspepsia. *Am J Gastroenterol* 1998;**93**:160–5.
- 25 Moss HE, Sanger GJ. The effects of granisetron, ICS 205–930 and ondansetron on the visceral pain reflex induced by duodenal distension. *Br J Pharmacol* 1990;**100**:497–501.
- 26 Delvaux M, Louvel D, Mamet JP, et al. Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 1998;**12**:849–55.
- 27 Zerbib F, Bruley des Varannes S, Oriola RC, et al. Alosetron does not affect the visceral perception of gastric distension in healthy subjects. *Aliment Pharmacol Ther* 1994;**8**:403–7.
- 28 Tack J, Wilmer A, Coulie B, et al. Influence of ondansetron on gastric tone and on the perception of gastric distention. *Gut* 2000;**46**:468–73.
- 29 Notivol R, Coffin B, Azpiroz F, et al. Gastric tone determines the sensitivity of the stomach to distension. *Gastroenterology* 1995;**108**:330–6.
- 30 Tack J, Piessevaux H, Coulie B, et al. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 1998;**115**:1346–52.
- 31 Tack JF, Janssens J, Vantrappen G, et al. Actions of 5-hydroxytryptamine on myenteric neurones in the gastric antrum of the guinea-pig. *Am J Physiol* 1992;**263**:G838–46.
- 32 Pan H, Galligan JJ. 5-HT_{1A} and 5-HT₄ receptors mediate inhibition and facilitation of fast synaptic transmission in enteric neurons. *Am J Physiol* 1994;**266**:G230–8.
- 33 Tonini M, Galligan JJ, North RA. Effects of cisapride on cholinergic neurotransmission and propulsive motility in the guinea-pig ileum. *Gastroenterology* 1989;**96**:1257–64.
- 34 Buchheit KH, Buhl T. Prokinetic benzamides stimulate peristaltic activity in the isolated guinea-pig ileum by activation of 5-HT₄ receptors. *Eur J Pharmacol* 1991;**205**:203–8.
- 35 Tack J, Broekaert D, Coulie B, et al. The influence of cisapride on gastric tone and the perception of gastric distension. *Aliment Pharmacol Ther* 1998;**12**:761–6.
- 36 Michel K, Sann H, Schaaf C, et al. Subpopulations of gastric myenteric neurones are differentially activated via distinct serotonin receptors: projection, neurochemical coding, and functional implications. *J Neurosci* 1997;**17**:8009–17.
- 37 Tack J. The physiology and the pathophysiology of the gastric accommodation reflex in man. *Verh K Acad Geneesk Belg* 2000;**62**:183–210.
- 38 Coulie B, Tack J, Sifrim D, et al. Role of nitric oxide in fasting gastric fundus tone and in 5-hydroxytryptamine-1 receptor-mediated relaxation of the gastric fundus. *Am J Physiol* 1999;**276**:G373–7.
- 39 Tack J, Coulie B, Wilmer A, et al. Influence of sumatriptan on gastric fundus tone and on the perception of gastric distension in man. *Gut* 2000;**46**:468–73.
- 40 Tack J, Caenepeel P, Fischler B, et al. Hypersensitivity to gastric distention is associated with symptoms in functional dyspepsia. *Gastroenterology* 2001;**121**:526–35.
- 41 Tack J, Vos R, Caenepeel P, et al. Fundic tension receptors mediate perception in functional dyspepsia patients with hypersensitivity to gastric distention [abstract]. *Gastroenterology* 2001;**120**:A239.
- 42 Coulie B, Tack J, Janssens J. Influence of buspirone-induced fundus relaxation on the perception of gastric distention in man. *Gastroenterology* 1997;**110**:A767.
- 43 Tack J, Piessevaux H, Coulie B, et al. A placebo-controlled trial of buspirone, a fundus-relaxing drug, in functional dyspepsia: Effect on symptoms and gastric sensory and motor function [abstract]. *Gastroenterology* 1999;**116**:A325.
- 44 Azpiroz F, Malagelada JR. Perception and reflex relaxation of the stomach in response to gut distention. *Gastroenterology* 1990;**98**:1193–8.
- 45 Coffin B, Azpiroz F, Guarner F, et al. Selective gastric hypersensitivity and reflex hyporeactivity in functional dyspepsia. *Gastroenterology* 1994;**107**:1345–51.
- 46 Brikas P, Kania BF, Fioramonti J, et al. Central and peripheral serotonergic influences on viscerovisceral inhibitory reflex during duodenal distension in sheep. *Dig Dis Sci* 1993;**38**:1079–86.
- 47 Feinle C, Read NW. Ondansetron reduces nausea induced by gastroduodenal stimulation without changing gastric motility. *Am J Physiol* 1996;**271**:G591–7.
- 48 Talley NJ, Van Zanten SV, Saez LR, et al. A dose-ranging, placebo-controlled, randomized trial of alosetron in patients with functional dyspepsia. *Aliment Pharmacol Ther* 2001;**15**:525–37.