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-HT, 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-HT, agonist/weak 5-HT, 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, 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, agonist, reduces cholinergic tone to the stomach, thereby increasing the threshold for discomfort and reducing the severity of dyspeptic symptoms.

**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. 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 ofafferent projections to the CNS. Accumulating evidence supports the hypothesis that 5-HT is a neurotransmitter in the enteric nervous system (ENS). 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. Visceral sensation is modulated at different levels of the brain-gut axis. The neuroanatomical pathways involved in this process have been reviewed extensively. 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 manner 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. The role of 5-HT in visceral perception requires further investigation. Describing 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. 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, 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 serotonin reuptake inhibitors; 5-HT, serotonin.
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). 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. 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). 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.

Table 1: Overview of 5-HT receptors and their ligands

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Selective agonist</th>
<th>Selective antagonist</th>
<th>Non-selective agonist</th>
<th>Non-selective antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>B-OHDPAT</td>
<td>WAY 100365</td>
<td>Buspirone</td>
<td></td>
</tr>
<tr>
<td>1B</td>
<td>Sumatriptan</td>
<td>GR 55562</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1D</td>
<td>Sumatriptan</td>
<td>BRL 15572</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1F</td>
<td>LY 334370</td>
<td>MDL 100907</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2A</td>
<td>α-Me-5-HT</td>
<td>Ketanserin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mianserin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2B</td>
<td>α-Me-5-HT</td>
<td>BV 723C86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2C</td>
<td>α-Me-5-HT</td>
<td>Messulergine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SR 57227</td>
<td>Olanosetron</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorophenylbiguanide</td>
<td>Granisetron</td>
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<td></td>
<td></td>
<td>Alosetron</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Tropisetron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>BIM U8</td>
<td>GR 113908</td>
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<td></td>
<td>RS 67506</td>
<td>SB 204070</td>
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<td></td>
<td>ML 10302</td>
<td>RS 100235</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Tegaserod</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Prucalopride</td>
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</tbody>
</table>

Those suitable for use in humans are italicised.

SEROTONERIC 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. 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. Recently, we demonstrated that administration of the SSRI citalopram significantly lowered mechano- and chemosensitivity in healthy subjects. 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. The results of a relatively small study
(n = 19) showed that imipramine improved symptoms in these patients but chemo- or mechanosensitivity of the oesophagus was not investigated. 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. 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. Likewise, preliminary studies using the non-selective antagonists of 5-HT₃ and 5-HT₂ 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 distension.

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. However, in human studies this effect has only been observed in the lower part of the gastrointestinal tract. The selective 5-HT₃ antagonists alserstud and ondansetron do not appear to have any significant effects on sensitivity to gastric distension. 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. It is possible therefore that serotonergic ligands, which influence fasting and postprandial gastric tone, may also affect sensitivity to gastric distension.

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. 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-HT₃, 5-HT₁, 5-HT₂, and 5-HT receptors have all been identified on myenteric neurones in the guinea pig stomach.

Pretreatment with 5-HT₃ receptor antagonists was found to have no influence on fasting or postprandial gastric tone in healthy volunteers. However, activation of 5-HT, receptors, believed to be located presynaptically on nerve terminals of enteric cholinergic interneurones and motor neurones (fig 1), has been shown to enhance the release of acetylcholine from cholinergic nerve endings, resulting in increased contractility.

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. 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.

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-HT₃ receptors which are predominantly located on inhibitory motor neurones of the gastric myenteric plexus (fig 1). Recent studies have identified sumatriptan as a 5-HT₁ receptor agonist which interacts with nitrergic myenteric neurones in the guinea pig stomach and which induces gastric relaxation in cats and humans. In acute studies, sumatriptan has been shown to enhance the intragastric volumes needed to induce perception and discomfort in fasted healthy volunteers, and to normalise meal induced relaxation and improve symptoms of early satiety in patients with impaired postprandial accommodation.

A subset of patients with functional dyspepsia have hypersensitivity to gastric distension accompanied by more prevalent symptoms of pain, belching, and weight loss. 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.

The non-selective 5-HT₃ 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. 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-HT₃ receptor agonists, 5-HT₄ receptor agonists, and 5-HT₁ receptor agonists all appear to have beneficial effects in patients with functional dyspepsia and impaired accommodation. The 5-HT₁ and 5-HT₃ 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 stimulants. 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-HT antagonist. In humans, ondansetron reduces the sensation of nausea provoked by the combined stimuli of intraduodenal lipid infusion and gastric distension. As the drug does not alter gastric tone or sensitivity, it probably acts at duodenal vagal afferents.

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**Figure 2** Rationale for the use of selective serotonergic reuptake inhibitors (SSRIs) and the role of 5-HT in gastrointestinal sensorimotor function.
A recent study demonstrated a reduction in dyspepsia symptoms in patients treated with the 5-HT3 receptor antagonist alosetron.

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

References