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.
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>8-OH-DPAT</td>
<td>WAY 100365</td>
<td></td>
<td>Buspirone</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>KETANSERIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1G</td>
<td>α-Me-5-HT</td>
<td>MEL 100907</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1H</td>
<td>α-Me-5-HT</td>
<td>SB 200646</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1I</td>
<td>α-Me-5-HT</td>
<td>SB 204741</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2A</td>
<td>α-Me-5-HT</td>
<td>MESULERGINE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2B</td>
<td>α-Me-5-HT</td>
<td>SB 242084</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2C</td>
<td>α-Me-5-HT</td>
<td>RS 102221</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SR 57227</td>
<td>ODANSERON</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorophenylbiguanide</td>
<td>Granisetron</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aloseteron</td>
<td></td>
<td></td>
</tr>
<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>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RS 67506</td>
<td>SB 204070</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ML 10302</td>
<td>RS 100235</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tegaserod</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prucalopride</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Those suitable for use in humans are italicised.
Serotonergic modulation of visceral sensation

The 5-HT3 receptor may play a role in this response. That ondansetron increases oesophageal thresholds to distension implies that the improvement might have been associated with a 5-HT3 receptor antagonist. Studies in animals suggest that 5-HT3 receptors are putative mechanisms of the oesophagus not was investigated. However, the authors suggested that the improvement might have been associated with a 5-HT3 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, 5-HT4 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 antagonists 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 alosetron 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 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, 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-HT3 receptor agonists all appear to have beneficial effects in patients with functional dyspepsia and impaired accommodation. The 5-HT3 and 5-HT4 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 visco-visceral reflexes are predominantly mediated through vagal afferents and triggered physiologically by intestinal mechanical stimuli and by the presence of duodenal nutrients. 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. 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.
A recent study demonstrated reduction in dyspepsia symptoms in patients treated with the 5-HT3 receptor antagonist.

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.

REFERENCES
Serotonergic modulation of visceral sensation: upper gastrointestinal tract

J Tack and G Sarnelli

*Gut* 2002 51: i77-i80
doi: 10.1136/gut.51.suppl_1.i77

Updated information and services can be found at:
http://gut.bmj.com/content/51/suppl_1/i77

**References**

This article cites 44 articles, 12 of which you can access for free at:
http://gut.bmj.com/content/51/suppl_1/i77#BIBL

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/