

## VISCERAL PERCEPTION

# Pharmacotherapy: non-serotonergic mechanisms

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Antidepressants rapidly relieve pain in irritable bowel syndrome (IBS) and are effective at low doses. Noradrenaline reuptake inhibitors appear to be more effective than selective serotonergic reuptake inhibitors, suggesting that pathways other than those modulated by serotonin may be involved in visceral sensation. Visceral sensitivity is reduced by both centrally and peripherally acting opioids, suggesting the possible existence of an endogenous opioid deficiency in patients with IBS. The  $\alpha_2$  adrenoceptor antagonist clonidine, as well as somatostatin, oxytocin, and possibly amitriptyline have also been shown to act as visceral analgesics. As knowledge increases, there are undoubtedly many other possible targets, and new drugs currently undergoing development may provide future benefit in patients with IBS.

### SUMMARY

Antidepressants rapidly relieve pain in irritable bowel syndrome (IBS) and are effective at low doses. Noradrenaline reuptake inhibitors appear to be more effective than selective serotonergic reuptake inhibitors (SSRIs) suggesting that pathways other than those modulated by serotonin (5-HT) may be involved in visceral sensation. Visceral sensitivity triggered by rectal distension in humans has been shown to be reduced by both centrally (fentanyl) and peripherally acting opioids (fedotozine and possibly loperamide) suggesting the possible existence of an endogenous opioid deficiency in patients with IBS. Somatostatin has been shown to decrease perception of rectal distension in healthy volunteers and is thought to have a peripheral site of action. Octreotide and other selective somatostatin receptor agonists inhibit mechanoreceptors, and reduce responses to chemical mediators such as bradykinin. These findings suggest that somatostatin may play a role in afferent neurone transduction. The  $\alpha_2$  adrenoceptor agonist clonidine causes presynaptic hyperpolarisation, which diminishes neurotransmitter release, especially acetylcholine. Clonidine increases colonic compliance in volunteers: it also delays small bowel transit and reduces colonic tone and sensitivity to distension. Its sedative and analgesic properties suggest that it may have both central and peripheral actions. A non-sedating  $\alpha_2$  adrenoceptor agonist may provide future benefit in patients with IBS.

### INTRODUCTION

One of the main factors which drives patients with IBS to see a doctor is the severity of abdomi-

nal pain and discomfort. As in other branches of medicine, when dealing with pain it is useful to consider the degree of inflammation and whether the desired site of action of analgesia is central or peripheral. Rheumatoid arthritis is treated mainly with anti-inflammatory agents and corticosteroids: central actions are considered undesirable. In contrast, cancer pain, although also associated with tissue destruction and some inflammation, is often associated with fear and anxiety and so combining peripheral anti-inflammatory analgesics with centrally acting agents is often appropriate.

There is evidence that in some patients with IBS the condition is triggered by an episode of inflammation,<sup>1,2</sup> but for most patients, if there is inflammation, it is very low grade. Patients' requirements for a central as opposed to a peripherally acting drug to treat IBS vary considerably. Some have great anxiety and may benefit from sedative analgesic drugs while others have minimal psychological disturbance and would resent any central sedative effect.

This review focuses on agents that act peripherally (table 1). Drugs, such as corticosteroids, which augment endogenous mechanisms are often the most successful. It is therefore of value to explore how endogenous antinociceptive mechanisms might be augmented.

### PERIPHERAL ENDOGENOUS ANTINOCICEPTIVE MECHANISMS

Local tissue inflammation induced in rats with Freund's adjuvant is accompanied by an abundant presence of mRNA for pro-opio-melanocortin and pro-enkephalin. Inflammatory cells from these animals, including T and B lymphocytes, monocytes, and macrophages all stain intensively with  $\beta$  endorphin and met-enkephalin.<sup>3</sup> There is also upregulation of opioid receptors in the nerves that supply the inflamed region.<sup>4</sup>

Opioid receptors have been found on cell bodies in dorsal root ganglia, on the central terminals of primary afferent neurones, and also in peripheral sensory nerve fibres.<sup>5</sup> The importance of these local opioids is demonstrated by blocking their actions with the non-selective opioid antagonist naloxone. Injection of naloxone into the knee joint of patients undergoing arthroscopy produces a marked increase in pain, something that is not seen with the intravenous route, indicating

**Abbreviations:** CCK, cholecystokinin; CNS, central nervous system; DNIC, descending nociceptive inhibitory control; IBS, irritable bowel syndrome; NK1, neurokinin; SSRIs, selective serotonergic reuptake inhibitors; 5-HT, serotonin.

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**Table 1** Potential non-serotonergic therapeutic agents

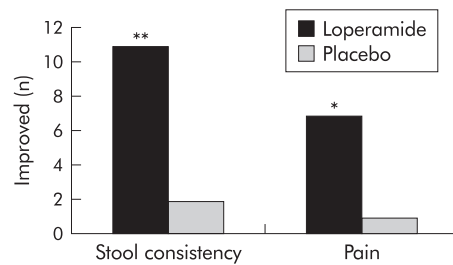
Therapeutic class	Drug therapy
Opioids	
κ agonist	Fedotozine
μ agonist	Loperamide (tramadol)
Somatostatin	Octreotide
α <sub>2</sub> Agonists	Clonidine, lidamidine
Low dose tricyclic antidepressants	Amitriptyline
Others	Oxytocin
	Tachykinin antagonists
	Cholecystokinin antagonist
	Anti-inflammatory agents

the importance of peripheral rather than central opioid effects.<sup>4</sup> Opioid receptors in the central nervous system (CNS) are located in the cingulate cortex and thalamus, both areas which are activated by painful stimuli.

The analgesic effect of placebo is undoubtedly important in IBS and may be mediated in part by endogenous endorphins. One of the first studies on this phenomenon examined patients two hours after molar extraction.<sup>6</sup> The McGill pain questionnaire was administered before and one hour after treatment which consisted of an ostentatious injection, which was said to contain an analgesic but which contained either fentanyl or saline. At the same time, without subjects being aware of it, a hidden infusion of either naloxone or vehicle alone was injected. When vehicle was injected, fentanyl was found to reduce pain as expected but so also did placebo. This placebo effect was reduced when naloxone was injected but was not totally abolished, indicating that a portion of placebo analgesia was due to endogenous opioids. Several further studies have been performed which, on balance, support these original findings.<sup>7</sup> It appears therefore that one of the effects of acute inflammation is to promote the release of cytokines which in turn trigger the release of bradykinin and prostaglandins thereby triggering the onset of hyperalgesia. In biological terms, this form of response is highly advantageous as it causes the organism to avoid further injury. However, if the inflammation becomes chronic, other mechanisms come into play.

These adaptive mechanisms include the local production of opioids and activation of descending nociceptive inhibitory control (DNIC) mechanisms originating in the mid brain.<sup>8,9</sup> Several authors have suggested that patients with IBS have a failure of DNIC mechanisms. One supporting study compared the sensitivity of the rectum to distension in patients with IBS and Crohn's disease.<sup>10</sup> Subjects with Crohn's disease suffered from ileitis alone and in common with IBS patients experienced diarrhoea and abdominal pain/discomfort. Phasic rectal distension demonstrated the well recognised finding of visceral hypersensitivity in patients with IBS but patients with Crohn's disease had normal sensitivity despite the fact that both groups showed exaggerated viscerosomatic referral compared with healthy controls. The autonomic response to rectal distension showed hyperreactivity in patients with IBS but hyporeactivity was seen in those with Crohn's disease, possibly due to activation of the DNIC system.

If impairment of the DNIC system is present in IBS, patients would be expected to benefit from exogenous administration of opioids, and intravenous fentanyl does indeed correct the hypersensitivity to rectal distension in subjects with IBS.<sup>11</sup> However, the use of centrally acting opioids is limited as patients with IBS are often intolerant of the central effects. Peripherally acting opioids, such as loperamide, are better tolerated than codeine, which acts centrally,<sup>12</sup> and offer potential advantages in the treatment of functional gastrointestinal disorders.



**Figure 1** Results of a three month clinical trial of loperamide compared with placebo. The dose was titrated to best effect and ranged from 2 to 8 mg per day. \* $p < 0.05$ , \*\* $p < 0.01$ . Reproduced with permission from Lavo and colleagues.<sup>14</sup>

### PERIPHERALLY ACTING OPIOIDS IN IBS

One of the most effective drugs currently available for the treatment of IBS is loperamide which improves the symptoms of urgency and borborygmi, delays small bowel and whole gut transit, reduces stool frequency, and improves consistency.<sup>13</sup> Loperamide also improves stool consistency and abdominal pain/discomfort in patients with IBS with diarrhoea (fig 1).<sup>14</sup> Encouraged by these findings a peripherally acting kappa ( $\kappa$ ) opioid receptor agonist fedotozine was developed.

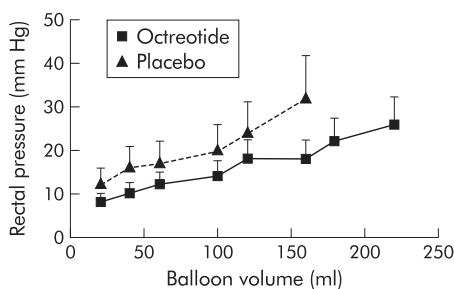
In animal studies, fedotozine was shown to inhibit the hypersensitivity to colorectal distension induced by acute colonic inflammation.<sup>15,16</sup> However, the drug proved disappointing in clinical practice. A large study of 238 patients with IBS showed that there was a statistically significant reduction in pain compared with placebo, but in clinical terms the size of the effect was small.<sup>17</sup> This trial was undertaken in a wide range of patients with IBS of varying severity, some of whom had very resistant disease. In retrospect it would have been better to exclude such patients as they rarely respond to any treatment.

### SOMATOSTATIN

Somatostatin is found in the primary afferent terminals in the superficial spinal dorsal horn and is released after noxious thermal injury.<sup>18</sup> Exogenous administration of somatostatin inhibits the firing of dorsal horn neurones in response to noxious cutaneous stimulation.<sup>19</sup> A case report suggests that epidural somatostatin can provide pain relief in patients with intractable pain,<sup>20</sup> and the hormone may also be effective against postoperative pain.<sup>21</sup> Intriguingly, levels of somatostatin-like immunoreactivity have been reported to be depressed in the cerebrospinal fluid of patients with chronic pain.<sup>22</sup>

Assessments of the effect of somatostatin on discomfort and pain induced by visceral distension in humans has been reported in several publications from the University of Michigan,<sup>23-25</sup> and confirmed by others.<sup>26</sup> In one of these studies intravenous administration of octreotide (100  $\mu$ g) was given 45 minutes prior to the assessment of rectal sensitivity in response to progressive inflation of a rectal balloon in a continuous ramp-like fashion at 100 ml per minute (fig 2).<sup>23</sup> Inflation was repeated three times in each of eight healthy volunteers and the thresholds noted. These studies indicated that although octreotide had no effect on compliance it reduced visceral sensitivity. This effect became maximal about one hour after injection.

Somatostatin is known to act at many sites in the brain but at least part of its effect is exerted on the primary sensory afferents. This is supported by the finding that spinal evoked potentials induced by rectal distension is significantly inhibited by subcutaneous administration of 100  $\mu$ g of octreotide.<sup>24</sup> It is also possible that there are subtle differences in the effect of somatostatin in different forms of IBS. Subcutaneous administration of octreotide (1.25  $\mu$ g/kg) to 10



**Figure 2** Octreotide 100 µg subcutaneously increased rectal compliance in eight patients with symptoms of diarrhoea compared with placebo. Reproduced with permission from Hasler and colleagues.<sup>23</sup>

patients with IBS with diarrhoea was shown to increase the thresholds for discomfort and pain, assessed using a barostat positioned in the descending colon.<sup>26</sup> As in previous studies, there was no effect on colonic tone, compliance, or response to a meal. A slightly different result was obtained in patients with diarrhoea predominant IBS in that subcutaneous administration of octreotide (100 µg) was found to increase rectal compliance which probably accounted for the rise in distension volumes required to reach perception and discomfort.<sup>25</sup>

Octreotide is known to inhibit the release of 5-HT from carcinoid cell tumours.<sup>27</sup> It is therefore possible that its effect in IBS with diarrhoea might be mediated via inhibition of the exaggerated release of serotonin from enteroendocrine cells that has been demonstrated in this subgroup of patients with IBS.<sup>28</sup> There is also an anecdotal report of relief of IBS symptoms in a patient with acromegaly who was treated with somatostatin.<sup>29</sup>

## CLONIDINE

The  $\alpha_2$  adrenoceptor agonist clonidine was initially developed as an antihypertensive agent. Clonidine is thought to act on presynaptic  $\alpha_2$  adrenoceptors linked to G proteins. Activation of these receptors acts via second messengers to open potassium channels, inducing hyperpolarisation of the nerve terminal and inhibition of neurotransmitter release.<sup>30</sup>

Administration of clonidine to rats has been shown to result in a dose dependant inhibition of the dorsal horn neurone response to noxious colorectal distension or cutaneous heating.<sup>31</sup> Several studies have shown that clonidine is an effective epidural analgesic when given either postoperatively<sup>32</sup> or during labour<sup>33</sup> when its lack of respiratory depression offers potential advantages compared with opioids. It has also been used as an intra-articular analgesic after arthroscopy.<sup>34</sup> However, direct evidence of its ability to reduce visceral pain is limited. Moreover, its central sedative effects severely limited its use as an antihypertensive agent.

Epidural administration of clonidine (75 µg) with 0.5% bupivacaine, 2% lidocaine, and noradrenaline has been shown to considerably increase the time to first analgesic request. Other studies have shown that clonidine can increase compliance and decrease sensation in healthy volunteers exposed to distension pressures ranging from 8 to 32 mm Hg.<sup>35</sup> In addition to these findings, clonidine and the related drug lidamidine have both been shown to inhibit colonic transit. These two agents have different pharmacological effects: lidamidine inhibits prostaglandin induced gastrointestinal secretion<sup>36</sup> while clonidine prolongs intestinal transit.<sup>37-39</sup> Through its antisecretory effects, lidamidine has been shown to be equally successful as loperamide in treating patients with acute diarrhoea.<sup>40</sup> It has been shown to reduce stool frequency in IBS but it has no significant effects on the severity of abdominal pain/discomfort in these patients.<sup>41</sup> Recent data

suggest that clonidine reduces colonic sensation at dose levels (0.05 and 0.1 mg) that do not alter gastric or colonic transit.<sup>42</sup> Small doses are not associated with significant somnolence or hypotension and the results of clinical trials in IBS are awaited.

## ANTIDEPRESSANTS

Antidepressants are among the most commonly prescribed drugs for IBS. Evidence of their central action is well established, and in a recent meta-analysis the odds ratio for improvement in pain was 4.2, indicating that these are among the most effective agents in IBS therapy.<sup>43</sup> However, data with modern antidepressants, particularly specific SSRIs, is relatively sparse.

Antidepressants are commonly used in low doses and are believed to exert an analgesic rather than an antidepressant effect. A study by Max *et al* examined the analgesic actions of three antidepressants in patients with painful diabetic neuropathy.<sup>44</sup> The drugs tested were desipramine, predominantly a noradrenaline reuptake inhibitor, amitriptyline which inhibits both noradrenaline and serotonin reuptake, and fluoxetine, predominantly a SSRI. Interestingly, amitriptyline and desipramine, the older less selective antidepressants, were found to be significantly better analgesics than fluoxetine.

Direct evidence for a visceral analgesic effect of amitriptyline is conflicting. A study by Gorelick and colleagues<sup>45</sup> found no beneficial effect on rectal or oesophageal sensitivity even though perception of cutaneous stimulation was reduced. Another study demonstrated a small but significant increase in the pressure required to produce pain in patients with IBS.<sup>46</sup> Further investigation is therefore required before definite conclusions can be drawn.

## TACHYKININ ANTAGONISTS

Visceral nociception is associated with release of substance P in the spinal cord and also locally from the gastrointestinal mucosa where it facilitates the release of algogenic agents such as histamine and prostaglandins from mast cells.<sup>47</sup> It is therefore logical to consider the potential use of tachykinin antagonists in IBS. Oral administration of a single 50 mg dose of the neurokinin 1 (NK1) receptor antagonist CJ-11974 has been compared with placebo in seven patients with IBS.<sup>48</sup> Although the NK1 antagonist showed a trend towards increased pressure thresholds for discomfort following repetitive sigmoid distension, the effect was not statistically significant. However, subjects' emotional responses to rectosigmoid stimulation in terms of reduced anger ratings suggested that the central effects of CJ-11974 might potentially be beneficial in patients with IBS. Newly available tachykinin antagonists are also being tested.

## OXYTOCIN

Oxytocin is widely distributed in the CNS and spinal cord, and experimental studies indicate that it has antinociceptive properties.<sup>49, 50</sup> Oxytocin has been used in intractable cancer pain.<sup>51</sup> When evaluated in patients with IBS it significantly increased the barostat pressure at which first sensation was detected in the descending colon. It also increased the pressure required to induce pain but it had no effect on compliance.<sup>52</sup> In these studies the analgesic effect of oxytocin was not mediated through opioids and was not inhibited by naloxone.

## OTHER AGENTS

Cholecystokinin (CCK) is known to have an analgesic effect in experimental models and the CCK-A receptor antagonist loxiglumide significantly alleviates symptoms of IBS.<sup>53</sup> However, the effects of these agents on visceral sensation have not been assessed.



Other potential pharmacological interventions include drugs used in somatic pain, and the use of anticonvulsants such as carbamazepine and phenytoin. Clinical trials with these agents have yet to be undertaken in IBS.

## CONCLUSION

Visceral sensitivity, as assessed by rectal or colonic distension in humans, is reduced by both centrally and peripherally acting opioids. In clinical trials the specific  $\kappa$  agonist, fedotozine, was well tolerated but had a disappointing effect on IBS symptoms. The  $\alpha_2$  adrenoceptor antagonist clonidine, as well as somatostatin, oxytocin, and possibly amitriptyline have also been shown to act as visceral analgesics.

The agents shown to be tolerable and effective for IBS pain so far are antispasmodics, antidepressants, loperamide, 5-HT<sub>3</sub> antagonists, and 5-HT<sub>4</sub> agonists. As knowledge increases there are undoubtedly many other possible targets, and the new drugs currently undergoing development should ensure that this remains a very active area of research in the foreseeable future.

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