VISCERAL PERCEPTION

Centrally acting agents and visceral sensitivity

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The evidence relating to the site and mechanism of action of "centrally acting" agents which may affect visceral sensitivity is reviewed. Antidepressant drugs such as amitriptyline as well as the newer selective serotonin reuptake inhibitors are thought to act at the level of the CNS. Opiates, including morphine as well as compounds such as trimebutine or fedotozine designed for therapeutic use in irritable bowel syndrome, are effective in reducing visceral nociception. Cytokines in the CNS are known to be involved in the modulation of pain and there is also evidence to suggest that centrally acting cytokines may play a role in the production of visceral hypersensitivity. Consequently, they may provide an interesting target for future research.

SUMMARY

This paper reviews evidence relating to the site and mechanism of action of "centrally acting" agents which may affect visceral sensitivity. Antidepressant drugs such as amitriptyline as well as the newer selective serotonin reuptake inhibitors (SSRIs) are thought to act at the level of the central nervous system (CNS). There is increasing evidence that the peripheral effects of these drugs may contribute to their ability to attenuate somatic pain but there is no evidence that these compounds affect visceral sensitivity per se. Opiates, including morphine and drugs such as trimebutine and fedotozine, are effective at reducing visceral nociception, and recent data suggest that this occurs as a result of a peripheral action at the level of the dorsal root ganglia (DRG). One possibility is that visceral stimulation induces long term alterations in the CNS. Cytokines in the CNS are known to be involved in the modulation of pain and there is also evidence to suggest that centrally acting cytokines may play a role in the production of visceral hypersensitivity. Consequently, they provide an interesting target for future research.

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INTRODUCTION

The CNS as a target for pharmacotherapy of visceral hypersensitivity originates from experience in patients with irritable bowel syndrome (IBS). Abdominal pain or discomfort are major diagnostic criteria for this condition.[1] Hypersensitivity to gastrointestinal distension plays an important role in the pathophysiology of IBS and has been considered as a biological marker for the disorder.[2] This was demonstrated for the first time in 1973 by sigmoid distension[3] and was subsequently confirmed in the rectocolonic,[4 5] gastric,[6] and oesophageal[7] regions.

There are several sources of evidence for a role of the CNS in hypersensitivity to gastrointestinal distension. Firstly, rats displaying genetically high levels of anxiety have been shown to display hypersensitivity to colorectal distension.[8] This evidence is supported by numerous human studies which have highlighted interactions between psychological factors and visceral sensitivity. For example, mental stress associated with anxiety has been shown to increase the sensation of gas in the transverse colon,[9] and the perception of jejunal distension has been shown to be reduced during periods of distraction and increased during periods of attentiveness.[10]

The relationship between visceral sensitivity and cortical integration of painful messages has been demonstrated in a more concrete manner with brain imaging techniques. The anterior cingulate cortex (ACC) has been identified as being involved in pain and its affective responses. Using positron emission tomography scanning to detect local changes in blood flow, it has been shown that painful rectal distension activates the ACC in healthy volunteers whereas in patients with IBS it activates the left prefrontal cortex.[11] Another study, using functional magnetic resonance imaging to measure local changes in blood oxygenation, has shown that in healthy volunteers the ACC is activated in the same manner for both painful and non-painful rectal distension, but in patients with IBS the degree of activation is greater for painful than for non-painful distension.[12] Despite the differences between the two studies, both emphasise that functional abnormalities in cortical centres are involved in pain integration in patients with IBS.

ANTIDEPRESSANTS

Tricyclic antidepressants are widely used in the treatment of IBS.[13] The efficacy of these compounds is related to the high prevalence of psychosocial factors in patients with this condition. However, most placebo controlled psychotropic drug trials in IBS indicate that in addition to producing global improvement or beneficial effects on diarrhoea or nausea, tricyclic antidepressants also reduce the severity of abdominal pain.[14–17] Experimental models of somatic pain

Abbreviations: ACC, anterior cingulate cortex; BBB, blood-brain barrier; CNS, central nervous system; DRG, dorsal root ganglia; IBS, irritable bowel syndrome; IL, interleukin; NTS, nucleus of the tractus solitarius; PVN, paraventricular nucleus; SSRIs, selective serotonin reuptake inhibitors; TNF-α, tumour necrosis factor α.

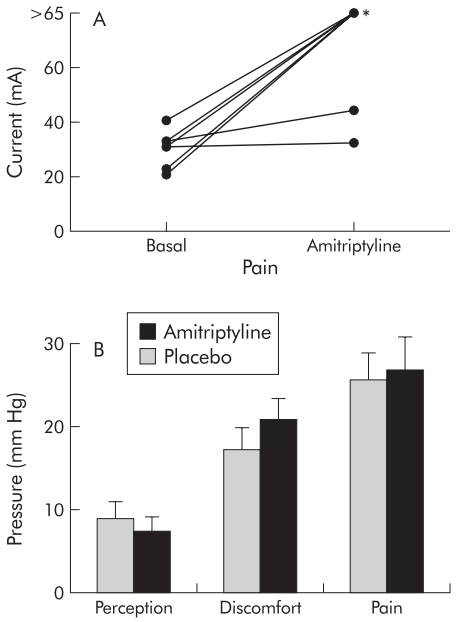

Figure 1 (A) A 21 day treatment with amitriptyline in healthy volunteers increased cutaneous electrical current to induce moderate pain. *p<0.05. Modified from Gorelick and colleagues.[20] (B) Amitriptyline did not significantly modify perception, discomfort, or pain thresholds to rectal distension. Modified from Gorelick and colleagues.[20]

including thermal, mechanical, or electrical stimuli studies indicate that antidepressants reduce pain perception.[18] In placebo controlled studies these drugs reduce pain associated with several somatic pain syndromes, including diabetic neuropathy, post-herpetic neuralgia, tension headaches, and fibromyalgia. In each case the effect on pain is not necessarily related to an effect on mood.[19]

Studies of the effects of antidepressants on visceral sensitivity are rare and the existing data are controversial. Gorelick and colleagues[20] confirmed that amitriptyline 50 mg/day for 21 days increases the thresholds for moderate discomfort and moderate pain elicited by cutaneous electrical stimulation in healthy volunteers (fig 1A) but they found no effect on the perception of rectal or oesophageal distension, and amitriptyline did not alter rectal or oesophageal compliance (fig 1B). Another volunteer study[21] indicates that imipramine, at increasing doses from 25 to 75 mg/day for 13 days, is unable to modify the volume threshold of oesophageal distension at first sensation but significantly increased the pain threshold. However, despite statistically significant differences in the pain threshold volumes between placebo and imipramine, the physiological significance of this finding remains questionable as mean volumes only increased from 21 ml with placebo to 23.5 ml with imipramine. Moreover, there was no drug effect on oesophageal compliance, and mean pressures at the pain threshold were not statistically different between imipramine and placebo (199.3 and 198.3 mm Hg, respectively).

Both of these published studies of the effects of antidepressants on visceral sensitivity were performed in healthy volunteers. The only data available for patients with IBS are limited.[22] This study showed that low dose amitriptyline 10–25 mg/day for six weeks increased the pressure thresholds necessary to induce pain using rectal distension and this change in threshold level appeared to be correlated with changes in symptom severity. However, an improvement over the control thresholds found in healthy volunteers was only achieved in four of 12 IBS patients in this study.

Traditional tricyclic antidepressants are not selective for inhibition of serotonin reuptake, and they display additional properties which have clinical effects in conditions other than depression. For example, some members of this drug class are known to inhibit neuronal reuptake of noradrenaline and dopamine, and amitriptyline as well as having antimuscarinic properties[23] is known to upregulate α_2 adrenoceptors.[24] These pharmacological effects all have the potential to influence intestinal fluid absorption and motility.

Tricyclic antidepressants and in particular SSRIs such as fluoxetine possess moderate affinity for 5-HT_3 receptors and act on the second messengers of 5-HT_4 receptors.[25] It is likely that these properties are related to the reductions in diarrhoea that have been reported in several clinical trials in patients with IBS,[14–16] and also to the ability of these drugs to increase gastrointestinal transit time.[26] Interestingly, it has been shown that administration of amitriptyline or fluoxetine to rats for a period of one month using non-psychiatric doses resulted in enhancement of the sensitivity of contractile intestinal muscle serotonin in vitro.[27] Antidepressants are generally considered to act at the level of the CNS but these results indicate that they may also have peripheral properties. This possibility is supported by studies showing that topical application of low concentrations of amitriptyline (1–10 nmol) cream or gel to the paws of rats has the ability to reduce pain induced by formalin administration.[28]

Other trials testing the efficacy of psychotropic drugs in patients with IBS have investigated combination treatment with anxiolytics and antidepressants.[14] Although there is no evidence to suggest that anxiolytic drugs affect either somatic or visceral pain, experimental data indicate that pregabalin, a novel compound displaying anxiolytic properties, reduces visceral hypersensitivity in the rat. This compound is related to gabapentin and is undergoing development for analgesic, anxiolytic, and anticonvulsant properties. Pregabalin interacts with calcium channels: it readily crosses the blood-brain barrier (BBB) and is very likely to have a central mechanism of action.[29] Experimental studies have shown that pregabalin also has the ability to reduce rectal hypersensitivity to distension induced by septic shock.[30] However, there was no evidence for a relationship between the efficacy of the compound on visceral hypersensitivity and its anxiolytic properties.

OPIATES

Opiates are the most widely recognised class of compounds that display efficacy against pain. The conventional view is that they act at opioid receptors located in the CNS, especially at the dorsal horn of the spinal cord. Trimebutine and fedotozine are two opiate compounds which have demonstrated efficacy in the treatment of IBS.

Trimebutine was originally considered to be an opiate compound because its effect on intestinal motility in dogs was reversed by naloxone.[31] It was subsequently classified as a weak opioid receptor agonist, mainly acting at the μ receptor.[32] Trimebutine has been found to be effective against hyperalgesia to rectal distension induced by inflammation or stress.[33] However, there is no evidence to indicate that the drug acts at the level of the CNS, and it seems unlikely that the compound crosses the BBB. Instead, trimebutine has been shown to interact with sensory neurones of the DRG and the drug has also been found to have local anaesthetic activity which is 17 times more potent than that of lidocaine.[34]

Fedotozine is a κ receptor agonist[35] which has been found to be effective in the treatment of abdominal pain and bloating associated with IBS.[36] It has been shown to increase discomfort thresholds to gastric distension in healthy volunteers,[37] and to colonic distension in patients with IBS.[38] Evidence from several experimental studies in animals indicates that fedotozine influences visceral sensitivity.[39–41]

The efficacy of fedotozine against noxious visceral stimuli has been confirmed in an elegant manner in rats.[42] Intraperitoneal administration of acetic acid induces the expression of

Fos, which is a marker of neuronal activation. This occurs in the thoracolumbar region of the spinal cord as well as in numerous central structures, including the paraventricular nucleus (PVN) of the hypothalamus. Fedotozine was shown to significantly decrease the immunoreactivity of Fos in the spinal cord and PVN of rats. This effect was thought to be mediated by κ receptors as it was reversed by the kappa opioid antagonist norbinaltorphimine. The observation that fedotozine was inactive against visceral pain induced by colonic distension when administered by the intracerebroventricular route suggests that its action is peripheral.[41] In another study, fedotozine was shown to be more active when administered by intrathecal than by intravenous routes in a study where neuronal responses to colorectal distension were recorded in the dorsal horn of the lumbosacral spinal cord, suggesting that the drug does have a central action at least at the level of the spinal cord.[43] Thus clear evidence of a central effect of either of these two opiate receptor agonists has yet to be obtained.

In addition to the specific cases of trimebutine and fedotozine, the question arises as to whether or not opiates in general act centrally to reduce visceral sensitivity. Morphine, which is considered as a prototype opiate agonist, has been shown to abolish pain induced by jejunal distension, as assessed by decreases in blood pressure in anaesthetised rats.[44] In conscious rabbits, morphine shows greater efficacy at reducing the pain response to rectal distension (assessed by behavioural parameters) when it is administered by the intrathecal route than when given intramuscularly. This suggests that morphine has a central action at the spinal cord level.[45] However, the proposition of a central action is not demonstrated unequivocally by this study as even though the same amount of morphine was administered by the two routes, it is likely that a greater concentration of morphine is achieved in the spinal cord after intrathecal administration than at the peripheral level after intramuscular administration. An argument against a central action of morphine is upheld by the finding that the ability of intraperitoneal morphine to reduce abdominal acetic acid induced writhing is antagonised by intraperitoneal administration of a quaternary derivative of naloxone which does not cross the BBB.[46] Conversely, the antidiarrhoeal opiate agonist loperamide has very poor penetration across the BBB with less than 0.04% of the compound being found in the brain one hour after oral administration,[47] but despite its selective peripheral action, loperamide has been shown to reduce pain in different models of somatic hyperalgesia in rats.[48] In fact, intraperitoneal loperamide has been found to be nearly as potent as morphine at reducing pain in the acetic acid writhing test (fig 2).[46]

Several placebo controlled trials have demonstrated the efficacy of loperamide in the treatment of IBS.[49–52] These trials indicate that improvements in diarrhoea (stool consistency and urgency) seen with loperamide are accompanied by a global reduction in pain intensity. In one study[52] loperamide was found to cause nocturnal pain which was not observed with placebo. Loperamide has also been shown to induce symptoms of IBS, including bloating, pain, and rectal dissatisfaction when administered for six weeks to healthy volunteers.[53] Nocturnal pain induced by loperamide may be attributed to its effect on motility as frequent high amplitude contractions have been described at the level of stomach, small intestine, and colon for several hours after administration of oral loperamide to dogs.[54] Patients with IBS have been shown to have lower than normal perception thresholds with respect to the sensation of intestinal contractions.[55] Alterations in intestinal motility in response to loperamide may also contribute to the nocturnal pain observed in patients with IBS.[52]

CENTRAL NEUROIMMUNE INTERACTIONS: A NEW TARGET?

An increasing body of evidence indicates that visceral stimulation can induce long term alterations in the CNS. This

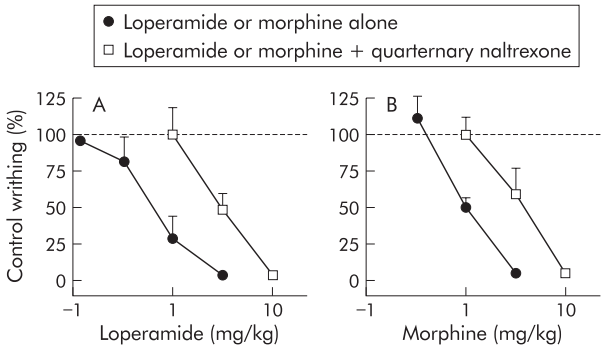

Figure 2 Comparative antinociceptive action of loperamide (A) and morphine (B) in reducing writhing induced by intraperitoneal acetic acid in mice. Loperamide, which poorly crosses the blood-brain barrier displays a potency similar to that of morphine. The selective peripheral opiate receptor antagonist, quaternary naltrexone, similarly antagonises the effects of loperamide and morphine. These data suggest a peripheral action of opiates in reducing pain induced by peritoneal irritation. Modified from Takasuna and colleagues.[46]

evidence originates from studies showing that intestinal stimuli induce expression of immediate early gene encoded proteins such as c-Fos which are involved in the signal transduction cascade that links extracellular events to long term intracellular adaptations. c-Fos has been shown to be expressed in the spinal cord[56] and in limbic structures[57] after colorectal distension, and in the nucleus of the tractus solitarius (NTS) after gastric distension.[58] c-Fos is also expressed in the spinal cord and brain stem sites after colonic inflammation induced by mustard oil,[59] and in the NTS at the onset of the jejunal inflammation induced by the nematode *Nippostrongylus brasiliensis*.[60] However, the nature of long term intracellular adaptation, in terms of neuromediators or receptors induced by c-Fos, is largely unknown which prevents us from being able to define the pharmacological targets for the sites activated by visceral stimuli.

There is a small but growing body of evidence to show that cytokines may play a role in the central control of the effects of visceral stimuli. Certain cytokines, which are released by activated macrophages and lymphocytes, are also present in the CNS. For example, the brain stem has been shown to have a high density of tumour necrosis factor α (TNF-α).[61] Gastric distension is known to activate neurones in the NTS, and local microinjection of TNF-α has been shown to potentate the firing rate of NTS neurones in response to gastric distension.[62]

Prolonged (three hour) rectal distension in the anaesthetised rat induces expression of interleukin (IL)-1β in the brain.[63] Central expression of IL-1β is thought to be involved in a physiological mechanism as water secretion in the proximal colon induced by rectal distension is reversed by intracerebroventricular administration of an IL-1 receptor antagonist. This form of water secretion is also blocked by intracerebroventricular administration of indomethacin, indicating that prostaglandins are involved at a central level. These results indicate that rectal distension has the ability to trigger central mechanisms similar to those responsible for endotoxin induced fever, which involves an interaction between IL-β and prostaglandin E_2 in circumventricular organs such as the organum vasculosum of the lamina terminalis region. The central role of interleukins and prostaglandins is very unlikely to be explained by a leakage or passage of endotoxins through the distended colonic wall as it has been shown that colonic distension does not induce translocation of bacteria or endotoxins in humans.[64]

The primary role for cytokines and prostanoids in the CNS is to modulate somatic pain.[65] However, there is evidence to suggest that central cytokines may also be involved in visceral

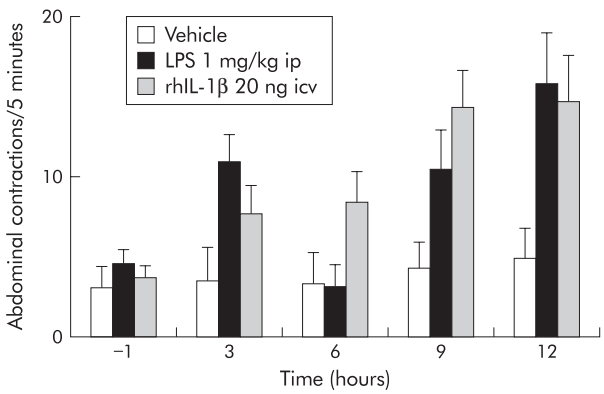

Figure 3 Role of central human recombinant interleukin 1β (rhIL-1β) in allodynia to rectal distension (0.4 ml) induced by lipopolysaccharide (LPS). LPS administered intraperitoneally (ip) induced delayed allodynia at 3, 9, and 12 hours after administration. Similarly, allodynia appeared 9 and 12 hours after intracerebroventricular (icv) administration of IL-1β. Modified from Coelho and colleagues.[66 67]

sensitivity. Intraperitoneal administration of endotoxins has been found to delay allodynia in response to rectal distension in rats by 6–12 hours (fig 3).[66 67] This form of allodynia can be reproduced by intracerebroventricular administration of IL-1 or TNF-α and abolished by intracerebroventricular administration of an IL-1 receptor antagonist or soluble TNF receptor. These results suggest cytokines in the CNS may play a role in the production of hypersensitivity to distension associated with infection. It remains to be seen whether visceral hypersensitive states, which are not associated with endotoxins, also involve brain cytokines, as is the case for somatic pain.

CONCLUSION

It is commonly thought that antidepressants and opiates are two classes of drugs which act at the level of the CNS to relieve visceral pain. While it is clear that antidepressants attenuate somatic pain there is no evidence that these compounds affect visceral sensitivity. Opiates, including morphine as well as compounds such as trimebutine or fedotozine designed for therapeutic use in IBS, are effective in reducing visceral nociception. However, their site of action at the level of the CNS has become questionable in the light of accumulating data which favour a peripheral site of action. The intensity of neuronal activation induced by visceral stimulation and its long term consequences confirms that the CNS remains a privileged target for reducing visceral hypersensitivity. Other studies indicate that central cytokines may provide an interesting target for future research. However, it is still too early to predict therapeutic efficacy via manipulation of this pathway.

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