The role of neurotransmitters in IBS pathophysiology: a literature review

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Objective: To determine if neurotransmitters have relevance in the pathology of irritable bowel syndrome (IBS).

Review methods: Electronic searches of literature from PUBMED, MEDLINE and EBSCO in October and November 2006 using the terms IBS, neurotransmitters, serotonin, CCK, mast cell, 5-HT, substance P. Some of the articles were only published in abstract form.

Review: Clinical studies performed on colon tissue of rodents and humans and trials on the effects of serotonin (5-HT) antagonists in IBS generally and rectal hypersensitivity are included. Two trials on cholecystokinin (CCK) were reviewed with regards to their impact in IBS. The most extensively researched was 5-HT often with a view to patenting medications or establishing new approaches to treatment of IBS. These have been invaluable in understanding the role of hormones in the disorder. IBS occurs more commonly in women and three studies recorded that women have an increased rectal sensitivity to distension. Substance P, a neuropeptide, has been found in higher levels in the tissue of IBS patients in two studies and may have a role in the pain of the disorder. Two studies observed the impact of extreme stresses such as sexual abuse, depression and explosive noise on colon motility. These stresses altered colon motility and rectal threshold. Trials on 5-HT antagonists and other IBS drug therapies were researched for appropriateness to the topic. Of the 29 studies on neurotransmitters, 24 were on humans or human tissue. Reviews of other research have also been included. The summary of research is included in Table 1.

Trials of herbal medicines on IBS were researched for general reference but not included. The emphasis of these studies is to establish efficacy rather than the pharmacodynamic relationship to neurotransmitter release in IBS. Symptoms were evaluated as a reduction in pain, discomfort and intestinal motility.

Conclusions: The impact of 5-HT is of significance in IBS. Trials on CCK are few, and of the two cited one had minor relevance to IBS symptoms. Many of the clinical trials are on the significance of 5-HT, propelled by pharmaceutical companies to find a patented drug for treatment. Whilst the 5-HT antagonists do have positive outcomes against placebo (ie: reduced rectosigmoid sensitivity, reduced bloating, reduced colon motility) the drugs tested had insignificant impact on the pain of IBS. Studies into mast cells have elucidated the impact of local neuropeptides on the pain mechanisms in IBS and this may be an area of further study. Prior inflammation may have a role is establishing alterations in immuno-reactivity in the colorectal mucosa.

Introduction

IBS is a chronic disorder of recurring symptoms including abdominal pain, feeling of discomfort and bloating with altered bowel habits. It can be divided in to IBS-D (diarrhoea dominant), IBS-C (constipation dominant) or alternating D and C and further in IBS-PI (post infective). Patients are categorised according to their symptoms and the absence of other organic disease of the colon. IBS is not well understood and many factors have been attributed to its occurrence, such as food allergies/intolerance, stress, genetic disposition, depression, central nervous system (CNS) disturbance and recently altered neurotransmitter release (Talley 2005, Santos 2005). IBS can occur following gastroenteritis or other inflammation (Talley 2005). Colon hypersensitivity is a common
symptom of IBS particularly in IBS-D (Chang 2006, Xiao 2004). Research has suggested that food intolerances and ultimately mast cell mediators may be responsible for such hyperalgesia (Santos 2005).

Originally considered a functional disorder, research into the role of neurotransmitters indicates a neurological origin (Aggarwal 2006). Ninety five percent of total body 5-HT is located in the GIT (Moura 2005). It is secreted by the enterochromaffin cells of the microvilli and it promotes peristalsis in the GIT. Patients with IBS-D have been found to have excess amounts of 5-HT (Pimentel 2004). Due to these findings research into 5-HT antagonists has explored drug therapies that attempt to remedy this excess. The development of 5-HT antagonists has been difficult due to toxicity of the drugs. They have proven to be only modestly effective over placebo and have little in the way of long term safety data (Talley 2005, Moura 2005). Most of the trials are of small number, over a period of weeks. They are invaluable in terms of the information they reveal regarding the pathology of IBS. One doctor warns that these medications should only be used when required and not long term (Moura 2005). The findings that the disorder is greatly affected by hormones and neurotransmitters gives a therapist a broader therapeutic range of treatment options.

Stress and food intolerances have been generally implicated in IBS. There have been concepts elucidated through research which suggest that stress and food intolerances may cause alterations in local gut hormones and the sensitising of mast cells. Allergenic reaction causes mast cells to overexcite enteric nerve endings (Guilarte 2006, Bischoff 2004) and this could explain visceral hypersensitivity, a symptom that occurs commonly in IBS-D particularly in women.

### Hormones implicated in IBS

#### Serotonin (5-HT)

Serotonin is a gut hormone implicated in the pathology of IBS. The microvilli cells of the GIT secrete 5-HT. The activity of 5-HT is concentrated in the GIT (95%) where it initiates peristalsis and induces contraction of the internal anal sphincter (Mulak 2006). Postprandial 5-HT is elevated in IBS-D patients (Pimentel 2004) and pain in IBS correlates with peak plasma concentrations of 5-HT (Hicks 2002). It has not been established why a patient would have more 5-HT receptors and 5-HT activity than another. It may be linked to a prior gastrointestinal infection. In a study of rectal mucosal enteroendocrine cells (EC) post enteritis infection, Spiller (2000) noted that 5-HT receptor containing ECs were increased after the first biopsy at 3 weeks. This increase in 5-HT is part of a primitive protective cleansing mechanism which induces vomiting and diarrhea, thereby clearing infective pathogens by copious secretions and increased motility. In the same study 5-HT receptors remained in excess in some cases for up to one year after the initial acute episode passed. Most of the studies of IBS-D showed an increase in 5-HT activity and those improved with 5-HT antagonists.

### Serotonin (5-HT) treatment in IBS

Allopathic treatment of visceral pain includes smooth muscle relaxants which are effective in IBS-D and abdominal pain but not IBS-C (Talley 2005). Tri-cyclic antidepressants at a low dose have been used for IBS but tend to be constipating (Talley 2005).

Trials on 5-HT antagonists are showing relatively moderate success in reducing bloating and reducing colon motility. In a 3 week preliminary drug study by Tack et al (2006), SSRI Citalopram® was effective in reducing bloating, abdominal pain and quality of life compared with placebo (Tack 2006). Mulak (2006), in a preliminary drug study, confirmed that sumatripin 5-HT agonist was active in reducing anal recto tension indicating that serotonin receptivity has a role in the regulation of rectal tone. The 5-HT antagonist alosetron was effective in inhibiting motor activity in the small and large bowel (Bush 2001). In particular this study confirmed that there are gender specific receptor sites for 5-HT antagonists in the large bowel. Females had more 5-HT receptors in the large bowel than males. Even though this study was on rodents, bowel hypersensitivity has been confirmed by Xiao (2004) and Chang (2006) with the use of inflatable distension balloon tests. The presence of more 5-HT receptors in the colorectal area gives some explanation as to why women suffer with IBS-D more than men. It is via this...
mechanism in particular that more trials are being conducted in humans rather than the preliminary animal testing.

Receptors for 5-HT are species specific. Many studies into drug efficacy have been carried out on animal tissue and then in patient tolerability of a particular 5-HT antagonist. Borman (2002) isolated a human specific receptor for 5-HT, 5-HT 2B which is specifically excitatory in humans and not found in animals. The receptors 5-HT 3 and 5-HT 4 are excitatory in guinea pigs, 5-HT 3 and 5-HT 1 receptors are excitatory in rats, where human 5-HT 2B receptors are highly reactive, more than 1000 times greater than other receptors. This will alter the approach of drug development and treatment by targeting human specific receptors. Many other studies are on animal tissue and may not be appropriate references because of interspecies variations.

Herbal treatment employs nervines, antispasmodics, carminatives and sedatives to deal with the symptoms of IBS (Braun 2005, Bian 2006, Bundy 2004).

**CCK**

CCK has a role in colon motility and sensory response in the GIT. It has been suggested that it may be involved in the IBS-C patient picture of bloating and pain. CCK regulates motor activity: gallbladder contraction and slower transit time (TT). The inhibitory effect of CCK on TT occurs in the ascending colon only. Receptors are in the longitudinal muscle of the colon, enteric nervous system, CNS and particularly mesenteric plexus. CCK acts on neurons and smooth muscle directly and its receptors are involved in pain perception. Hypersensitivity or exaggerated release of CCK increases with IBS symptoms (Varga 2004).

The role of CCK is not well understood in IBS however the possibility of patients having altered release has prompted a number of studies. Sjoland (1996) noted that IBS patients have a more prolonged release of CCK in a human controlled study however no other conclusions were extrapolated. A randomised double blind study of 36 patients trialling a CCK antagonist for IBS-C was not effective in increasing TT (Cremonini 2005). This study was on the effectiveness of a drug and not on the intricacies of CCK activity.

**Oxytocin**

Oxytocin is secreted in response to CCK release and it has increased the pain threshold in rat studies and visceral pain in IBS patients. Lower plasma levels of oxytocin have been reported in IBS and a study into the effect of administration on chronically constipated patients was undertaken in 2005 by Ohlsson et al. It had been demonstrated previously that intravenous oxytocin was effective in improving colonic motility, however this study involved nasal administration which was not significantly effective in increasing colon motility. It did however have a positive impact on depressed mood, abdominal pain and feelings of discomfort (Ohlsson 2005).

**Substance P - neuropeptide**

In a study of interstitial cystitis and IBS occurring simultaneously in women, elevated levels of substance P and increased mast cell counts of three times the norm were observed (Pang 1996). In this study mast cells were mostly concentrated around nerve endings. In another study by the same author on interstitial cystitis, substance P has been shown to initiate mast cell secretion (Pang 1995, 1996). It is theorised that substance P and the pain of IBS are related (Bischoff 2004, Pang 1996). This has also been suspected by other researchers to have a role in gut hypersensitivity (Guilarte 2006, Santos 2005, Delvaux 2002, Dong 2003). Pang also noted that estradiol enhances mast cell secretion by substance P in the bladder and that it may have a similar mechanism in the female colon. This may explain why women have more hypersensitivity generally in IBS. A study on calcium channel blockers for the treatment of IBS (Lu 2000) did not confirm that substance P or neuropeptide Y had any effect on IBS pathology. This might be an area of further study.

**Mast cells and inflammation**

Mast cells initiate stress induced mucosal inflammation of the colon. They have a role in inflammation, leucocyte activation, antigen identification, phagocytosis and epithelial/vascular permeability. Intestinal mast cells have been affected by neuropeptides such as Substance P in animal studies and their close proximity to nerve endings has made them suspected instigators of IBS.
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symptoms such as pain and hypersensitivity (Bischoff 2004, O’Sullivan 2000, Saavedra 2005).

There is an increase of mast cell mediators due to presence of allergens, resulting in increased water secretion and increased epithelial permeability to albumin, thought to be responsible for abdominal symptoms in IBS (Saavedra 2005).

Mast cells may sensitise enteric nerve endings making them more susceptible to histamine and tryptase. Their role in colon hypersensitivity has been linked to mast cells adjacent to nerve endings (Santos 2004, Delvaux 2002, Guilarte 2006). Saavedra (2005) observed in a controlled in vivo trial that chronic intestinal dysfunction in rats coexists with an increased mast cell count. Rats were exposed to food allergens which resulted in allergic sensitisation and the changes in mast cells were noted. He believes that motility alterations could be related to over excited mast cells rather than an increase in mast cells.

However in the first human trial (in vitro) Bischoff (2004) found that human mast cells did not produce histamine, sulphidoleukotrienes or tumor necrosis factor (mediators) after the application of substance P even at different concentrations. In the same study it was found that mast cells previously sensitised by an allergen or type I hypersensitivity reaction did have an increase in mediator production. This finding is in line with that of other examiners (Santos 2005, Delvaux 2002, O’Sullivan 2000, Saavedra 2005). The study by Bischoff was well conducted but involved in vitro human tissue and may not have shown the activity of in vivo mechanisms. He makes the point that in vivo tissue may activate mast cells.

Spiller et al (2000) recorded no significant increase in mast cells post an acute infection of Campylobacter enteritis, in fact some mast cell numbers were reduced in some patients.

A study by O’Sullivan (2000) confirmed that IBS patients have increased numbers of MC. They studied the impact of inflammatory inducers such as stress and infection and found no other identifier of inflammation (lymphocytes, neutrophils, macrophages or plasma cells) other than increased MC count. O’Sullivan makes an interesting theory that IBS may be a systemic condition involving the mast cells. Increases in mast cell numbers in the bladder and airway have been reported in IBS patients (Pang 1995, O’Sullivan 2000).

Wang et al (2004) observed that patients developed IBS symptoms sometimes months after an acute GIT episode. Interleukin-1 (cytokine secreted by macrophages) remained active in excessive amounts in the rectal tissue of patients up to three months after an acute GIT episode. This prolonged response to stress in the GIT was also observed by Spiller (2000). He considers that T lymphocytes may have a role in neuromuscular function by mediating changes and that alterations in the colorectal mucosa can lead to persistent, inflammatory and enteroendocrine dysfunction post infection.

**Rectal hypersensitivity**

Abnormal bowel patterns and heightened bowel sensitivity are common in IBS patients (Chang 2006, Xiao 2004, Gutherie 2004, Rutkowska 2006, Vege 2004). Visceral or colorectal hypersensitivity may be a marker of IBS (Dong 2004). Whilst pain is often a co-symptom of altered TT and hypersensitivity, it is unclear whether pain is associated with altered TT or sensory hypersensitivity.

IBS patients show a higher degree of self analysis of bowel symptoms and in some cases a preoccupation with their disorder (Gutherie 2004, Vege 2004). In dilation studies patients evaluate their own level of discomfort and this may not be the most appropriate or consistent indicator. In these studies it has been shown that IBS patients perceived alterations in bowel functions even when intestinal motility was normal (Mulak 2006). It is difficult to assess subject perceptions.

Distension studies have been successful in evaluating the effects of patent drugs or bowel tone. In a study by Mulak (2005) a sumatripan 5-HT agonist injection was effective in reducing anal threshold sensation, and the use of balloon distension test was imperative in gaining clinical outcomes.

Studies by Xiao (2004) and Chang (2006) also used distension balloons to evaluate hypersensitivity and pain in IBS and found females had a significantly greater occurrence of both. Here the subjectivity of the patient may have influenced the outcome. It has been found the IBS-C patients do not have the same
hypothesising to rectal distension nor do males compared with females (Xiao 2004).

Rectal and visceral hypersensitivity is poorly understood. Links have been theorised to prior intestinal infection which may create an environment of low grade inflammation where mast cell secretions can sensitise nerve endings (Spiller 2000, Wang 2004). It has been shown that mast cells are increased in IBS and concentrate at nerve endings in human and rat biopsies (Pang 1996, Dong 2003, O’Sullivan 2000, Saavedra 2005).

Furthermore it has been shown in one rat study that it is the degranulation rate of mast cells that is of significance (Lu 2000).

It could be via mast cell activation that the mechanism of pain of IBS is initiated rather than lumenal distension. Mulak (2006) reported increased anal threshold to pressure but not significant reduction in pain during a drug trial of a 5-HT agonist, indicating that reduced anal resting pressure did not alter the level of pain.

Gender differences in IBS

Physiological and psychological factors have been suggested to explain the higher incidence of IBS in women, although it is uncertain what these might be. The impact of female hormones, particularly in the follicular phase, on GIT hormones and anorectal sensitivity has been referred to but not fully investigated. There are drugs for IBS-D which are specifically efficacious for females (Bush 2001, Kermod-Scott 2000).

Originally it was thought there was no alteration in motor activity for male and female colon tissue, however through the development of IBS drugs these differences have been illustrated. Even though much of the research is on rat colon tissue, it has been observed in the trial of drugs on humans that women have selective efficacy for the 5-HT antagonist alosetron (Chang 2006, Bush 2001, Nozu 2006).

In the study of female mouse tissue, alosetron reduced motor activity 100 times more than that of male tissue (Bush 2001).

It is as a result of this evidence that females may have distribution of receptors vastly different from males. Sensitivity is one factor that is predominant in women and this is often measured in terms of a lowered threshold to rectal distension with a higher incidence of pain, discomfort and diarrhea (Xiao 2004).

Emerging concepts

IBS often occurs alongside other symptoms such as migraine, headache, lumbago, dysuria, insomnia, chronic fatigue syndrome, fibromyalgia, anxiety, chronic stress and depression (Mulak 2006, Moura 2005, Mu 2006). There may be a link between these symptoms and those of IBS and the role of serotonin in the GIT (Mulak 2006, Crowell 2004). A study showed that serotonin activity was normal on the CNS of IBS patients (Gorard 1996).

The mast cell connection suggests a systemic disorder where there are increases in the number of mast cells in other tissues also (O’Sullivan 2000). Hypersensitivity reaction instigates mast cell activity and its effect in other tissues may have a diagnostic application (Pang 1996, O’Sullivan 2000). The overlap of fibromyalgia, IBS and depression has also been made with regards to low levels of oxytocin. Whilst these disorders do occur individually they have a similarly neurological deficit.

Conclusion

In this review there is evidence to suggest there is local hormone activity of 5-HT. It is of particular significance in IBS-D where it has been shown to be excitatory, increasing the symptoms of increased motility. Research is limited to the design of drugs to antagonise the action of 5-HT. Mast cell activity remains a contentious issue. Most studies show an increase in the number of mast cells in the ileum, some show no changes at all.

There is however enough evidence to support the hypothesis that they have an effect on pain perception and hypersensitivity of the colon. Mast cells may also have a role in the maintenance of persistent immune response and low grade inflammation as demonstrated by post infective studies.

Allergenic response has been shown to increase T cells, enteroendocrine cells and mast cell secretions
which may have a role in post infective IBS, food intolerances or chronic stress.

Animal studies, whilst they were well conducted, focused on in vitro tissue as did many of the human trials on neurotransmitters. Living organisms react differently to in vitro tissue due to the interplay of other hormones. Interpretation of animal studies must be done with great care. Research into 5-HT has recently found human specific receptors in the colon and this highlights the obvious fact that comparisons cannot be too heavily drawn between laboratory animals and humans. Human testing is required in the area of the immunological impact on neurotransmitter activity in the dysfunctional colon.

The sample sizes for studies were small, and in only one case histology was conducted over one year. It would be necessary to evaluate neurotransmitter activity over longer time periods of time in the case of post allergic responses and chronic stress.

**Table 1**

Research on human and animal studies summarising neurotransmitter activity in the colorectal mucosa

<table>
<thead>
<tr>
<th>Topic</th>
<th>Reference</th>
<th>Design</th>
<th>Sample</th>
<th>Evidence</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of methane on 5-HT release (full)</td>
<td>Pimentel 2004</td>
<td>Human, blind</td>
<td>18</td>
<td>++</td>
<td>Methane link to constipation via serum 5-HT levels</td>
</tr>
<tr>
<td>Altered CCK, motilin in IBS (abstract)</td>
<td>Sjolund 1996</td>
<td>Const, study, human</td>
<td>29</td>
<td>++</td>
<td>Fats &gt; and prolong CCK release in IBS</td>
</tr>
<tr>
<td>Effect of SSRI in IBS symptoms (abstract)</td>
<td>Tack 2006</td>
<td>DBP crossover human</td>
<td>23</td>
<td>+</td>
<td>SSRI improved pain, bloat compared to placebo</td>
</tr>
<tr>
<td>5-HT agonist drug test (abstract)</td>
<td>Thervance 2006</td>
<td>DBPC phase I human</td>
<td>41</td>
<td>+</td>
<td>5-HT agonist mildly improved colon motility in healthy patients</td>
</tr>
<tr>
<td>Effect of auditory stress on GIT hormones (full)</td>
<td>Mu 2006</td>
<td>In vivo rodent</td>
<td>64</td>
<td>++</td>
<td>Explosive/loud noise = stress=altered gut hormone secretion and transit time</td>
</tr>
<tr>
<td>Ca channel blocker in IBS-D (abstract)</td>
<td>Lu 2000</td>
<td>RB human</td>
<td>91</td>
<td>+/-</td>
<td>Substance P and neuropeptide Y are not significant in the pathogenesis of IBS</td>
</tr>
<tr>
<td>CCK antagonists for IBS females (abstract)</td>
<td>Cremonini 2005</td>
<td>RBP human</td>
<td>36</td>
<td>-</td>
<td>CCK antagonist did not alter TT overall</td>
</tr>
<tr>
<td>Function of 5-HT in CNS of IBS patients (abstract)</td>
<td>Gorara 1995</td>
<td>Unblind open label human</td>
<td>39</td>
<td>-</td>
<td>CNS 5-HT pathways are normal in IBS</td>
</tr>
<tr>
<td>Alosetron, 5-HT antagonist in IBS :gender specific responses (full)</td>
<td>Bush 2001</td>
<td>In vivo rodent drug trial tissue</td>
<td>++</td>
<td></td>
<td>Female specific efficacy of drug. Maybe due to receptor distribution in ileum</td>
</tr>
<tr>
<td>Light impact on biorhythm of IBS patients (abstract)</td>
<td>Rutkowska 2006</td>
<td>Open experimental</td>
<td>8</td>
<td>++</td>
<td>Intense light improved IBS-D and IBS-C symptoms</td>
</tr>
<tr>
<td>5-HT agonist in IBS rectal function (full)</td>
<td>Malak 2005</td>
<td>RB PC crossover human</td>
<td>22</td>
<td>++</td>
<td>Drug reduced visceral hypersensitivity</td>
</tr>
<tr>
<td>Rectal hypersensitivity in IBS (full)</td>
<td>Xiao 2004</td>
<td>Open pilot semi blind</td>
<td>30</td>
<td></td>
<td>A reduced sensory threshold exists in IBS-D and females: males</td>
</tr>
<tr>
<td>Functional GI disorders and sleep disturbances (full)</td>
<td>Vege 2004</td>
<td>Population study</td>
<td>2269</td>
<td>+</td>
<td>IBS-D and sleep disturbances occur simultaneously with significance</td>
</tr>
<tr>
<td>Study Description</td>
<td>Author</td>
<td>Study Type</td>
<td>Result(s)</td>
<td>Findings</td>
<td></td>
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<td>----------------------------------------------------------------------------------</td>
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<td>------------------</td>
<td>-----------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Rat colonic afferent fibres have 5-HT receptors (full)</td>
<td>Hicks 2002</td>
<td>In vivo rodent</td>
<td>++</td>
<td>Colonic spinal nerves have 5-HT receptors. Role undetermined</td>
<td></td>
</tr>
<tr>
<td>Psychological state and rectal threshold in IBS (full)</td>
<td>Guthrie 2004</td>
<td>RCT Human</td>
<td>257 +</td>
<td>Sexual abuse/anxiety/depression leads to lower rectal threshold</td>
<td></td>
</tr>
<tr>
<td>5-HT agonist for IBS-C (abstract)</td>
<td>Nurbhai 2005</td>
<td>Phase I RBPC</td>
<td>Human</td>
<td>Established drug efficacy and tolerance</td>
<td></td>
</tr>
<tr>
<td>Women have an increased rectosigmoid sensitivity</td>
<td>Chang 2006</td>
<td>R human</td>
<td>84 +</td>
<td>Women have a perceived sensitivity with distension</td>
<td></td>
</tr>
<tr>
<td>Mast cell, Substance P in IBS (abstract)</td>
<td>Pang 1996</td>
<td>human Tissue biopsy</td>
<td>++</td>
<td>IBS patients have increased mast cell population and increased substance P at nerve endings</td>
<td></td>
</tr>
<tr>
<td>Post-dysenteric IBS and increased mucosal cells, T cells, gut permeability (full)</td>
<td>Spiller 2000</td>
<td>CT</td>
<td>31 +</td>
<td>Acute GIT episode can result in low grade inflammation of up to one year. Increased 5-HT in IBS</td>
<td></td>
</tr>
<tr>
<td>5-HT excites human colon tissue</td>
<td>Borman 2002</td>
<td>Human tissue</td>
<td>Tissue</td>
<td>Increased colon 5-HT 2B receptors - human specific Undetermined mechanism for 5-HT. Possible direct effect on smooth muscle</td>
<td></td>
</tr>
<tr>
<td>Sensitising to food allergies and effects on mast cells (full)</td>
<td>Saavedra 2004</td>
<td>Rat. CP</td>
<td>59 ++</td>
<td>Chronic intestinal dysfunction coexists with increased mast cells. Unconfirmed role of CCK on colon motility</td>
<td></td>
</tr>
<tr>
<td>Neuropeptides in human tissue as mediators of mast cells (full)</td>
<td>Bischoff 2004</td>
<td>Human Tissue</td>
<td>-/-</td>
<td>No release of histamine by Sub P. Preactivated cells (via IgE) receptor did increase mediator release</td>
<td></td>
</tr>
<tr>
<td>Increased mast cells in IBS (full)</td>
<td>O’Sullivan 2000</td>
<td>Human biopsy</td>
<td>Tissue</td>
<td>Mast cells significantly in crease in the ileocecum in IBS</td>
<td></td>
</tr>
<tr>
<td>Oxytocin in chronic constipation (full)</td>
<td>Ohlsson 2004</td>
<td>RDBPC</td>
<td>49 - -</td>
<td>Oxytocin did not improve colon motility, possibly due to nasal administration</td>
<td></td>
</tr>
<tr>
<td>Mast cells and substance P in IBS (abstract)</td>
<td>Dong 2003</td>
<td>Human biopsy</td>
<td>67 ++</td>
<td>Increased mast cells at ileoceleal junction in IBS</td>
<td></td>
</tr>
<tr>
<td>IBS-C have mast cell activation (abstract)</td>
<td>Guilante 2006</td>
<td>Human biopsy</td>
<td>34 +</td>
<td>Stress induces mast cell activity</td>
<td></td>
</tr>
<tr>
<td>Mast cells in IBS and visceral hypersensitivity (abstract)</td>
<td>Lee 2004</td>
<td>Rodent</td>
<td>+/-</td>
<td>Mast cells were not influenced. Degranulation rate of mast cells in IBS is increased</td>
<td></td>
</tr>
<tr>
<td>Visceral hypersensitivity in IBS (abstract)</td>
<td>Dong 2004</td>
<td>Human</td>
<td>63 +</td>
<td>Visceral hypersensitivity is a marker of IBS</td>
<td></td>
</tr>
<tr>
<td>Bacillary Dysentery as a causative factor in IBS (full)</td>
<td>Wang 2004</td>
<td>Cohort</td>
<td>295 +</td>
<td>Immune and nervous systems play a significant role in IBS pathology</td>
<td></td>
</tr>
</tbody>
</table>

* - negative result, + positive result in general, ++ positive result with proving of hypothesis.
References

Aggarwal V, Mc Beth J, Zakrzeskia J, Lunt M, Mac Farlane G. 2006. Epidemiology of chronic syndromes that are frequently unexplained: do they have common associated factors? Int J Epip 35;468-76.


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**Camellia sinensis**


