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TOPIC HIGHLIGHT

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Functional findings in irritable bowel syndrome

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Abstract

The pathophysiology of IBS is complex and still incompletely known. Both central and peripheral factors, including psychosocial factors, abnormal GI motility and secretion, and visceral hypersensitivity, are thought to contribute to the symptoms of IBS. Several studies have demonstrated altered GI motor function in IBS patients and the pattern differs between IBS subgroups based on the predominant bowel pattern. Few studies have so far addressed GI secretion in IBS, but there are some evidence supporting altered secretion in the small intestine of IBS patients. Visceral hypersensitivity is currently considered to be perhaps the most important pathophysiological factor in IBS. Importantly, several external and internal factors can modulate visceral sensitivity, as well as GI motility, and enhanced responsiveness within the GI tract to for instance stress and nutrients has been demonstrated in IBS patients. Today IBS is viewed upon as a disorder of dysregulation of the so-called brain-gut axis, involving abnormal function in the enteric, autonomic and/or central nervous systems, with peripheral alterations probably dominating in some patients and disturbed central processing of signals from the periphery in others.

Key words: IBS; Gastrointestinal motility; Visceral hypersensitivity; Gastrointestinal secretion; Intestinal gas; Brain-gut axis; Brain imaging; Autonomic nervous system

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INTRODUCTION

Irritable bowel syndrome (IBS) is characterized by abdominal pain and/or discomfort related to abnormal bowel habits[1]. It is probably the most common disorder encountered by gastroenterologists[2] and also the most common gastrointestinal disorder seen in primary care[3]. A problem in the management of IBS is that there are no structural or biochemical disease markers for these patients. Therefore, various diagnostic criteria have been used to define IBS in clinical practice and, more importantly, in research settings[1]. In the Western world, IBS appears to affect up to 20% of the population at any given time[4-6], although the prevalence figures vary substantially depending on the definition of IBS[7,8]. Due to its high prevalence and, for many patients, chronic nature and incapacitating symptoms the cost of IBS to society is substantial[9].

Despite being very common, the pathophysiology of IBS is far from understood. IBS has for a long time been considered a disorder of disturbed gastrointestinal motility, although uniform motility patterns in IBS have been hard to define. Moreover, motility findings have been difficult to relate to symptoms, especially abdominal pain[10,11]. Beginning in the early 1970s, but progressing rapidly in the 1990s were theories that visceral hyperalgesia independent of enhanced motility could explain the painful symptoms of IBS[12]. More recently, a more integrated model of brain-gut interactions proposes that the central and enteric nervous systems interact and modulate enhanced motility, abnormal sensation and autonomic reactivity: the brain-gut axis. In context with this model, psychosocial factors, rather than being a cause of IBS, are regarded as contributing to the predisposition, precipitation and perpetuation of IBS symptoms, and affect the clinical outcome[13]. However, despite the increasing knowledge of the pathophysiological and clinical aspects of IBS, there are a substantial number of unresolved issues.

During recent years the interest in finding relevant alterations in patients with IBS in the function of the gastrointestinal tract, as well as in the central and autonomic nervous system has increased. The trend is now that there is less focus on pure gastrointestinal alterations and instead more focus on interactions between exacerbating factors and gastrointestinal function, as well as on interaction between different parts of our nervous system and the gastrointestinal tract. This article will review the literature

on findings in IBS patients supporting disturbed function in the gastrointestinal tract as well as its interaction with the central and autonomic nervous systems.

ALTERED GASTROINTESTINAL MOTILITY

Esophageal and gastric motility

Most studies of motility in functional bowel disorders have focused on the large and small bowel, although there are also reports on disturbed motility in the esophagus and the stomach. Patients with IBS demonstrate, for instance, lower pressure in the lower esophageal sphincter and more esophageal contraction abnormalities than healthy subjects[14]. Furthermore, patients with contraction abnormalities in the esophagus often report symptoms compatible with IBS[15]. There are several studies of gastric emptying in patients with IBS. These have come to somewhat different conclusions, with some of the older studies being unable to detect an abnormality[16-18], whereas some of the more recent studies found abnormal gastric emptying in at least a subset of IBS patients[19-22]. Moreover, the presence of gastroparesis in IBS was found to be related to small bowel dysmotility[23]. In a recent large-scale study, delayed gastric emptying was found in IBS patients with overlapping dyspepsia, but not in those without dyspeptic symptoms[24]. Some studies have also used electrogastrography (EGG) in patients with IBS finding a nice correlation between lack of increased postprandial EGG amplitude and delayed gastric emptying in a subset of IBS patients[25], whereas another study found EGG abnormalities only in IBS patients with concurrent dyspeptic symptoms[26]. The conclusion of these studies seems to be that altered esophageal and gastric motor function is more related to the presence of upper GI symptoms than to IBS per se, even though a significant overlap between upper GI symptoms and IBS exists[27].

Small intestinal motility

The motor patterns of the small bowel in man are rather well characterized[28], but marked inter- and intraindividual variations make interpretation difficult[29,30]. In the late 1970s technological advances made it possible to accurately record small bowel motility in man. Thompson and co-workers, using a radiotelemetry capsule system, reported abnormal small-bowel motility in a patient with "irritable colon"[31], but a follow-up study using a similar recording system failed to confirm this[32]. Subsequent studies have focused on the periodicity of the migrating motor complex (MMC) (i.e. the interval between successive MMC cycles), as well as finding specific motor patterns in IBS and relating these patterns to symptoms. In diarrhea prone subjects, the periodicity of the MMC during daytime has been found to be shorter[33,34], but longer in IBS patients with predominant constipation[35], although these are not consistent findings[36,37]. Increased frequency of clustered activity has been found in some[33,34,38], but not all studies[36,37,39]. Of more interest perhaps, are correlations between symptoms in IBS patients and certain motility patterns, such as clustered activity (e.g. "discrete clustered contractions") and prolonged propagated contractions[33,34], but likewise, these findings have been partly[37] or totally[36] rejected by others. Furthermore, IBS patients have been found to have enhanced perception of physiological intestinal motility, such as the activity front[40]. There also appears to be a relationship between heightened sensitivity to distension of the small intestine and postprandial jejunal motor abnormalities in IBS patients[41]. An increased contraction frequency postprandially has been demonstrated in diarrhea and constipation predominant IBS[42], and in a study by Schmidt et al diarrhea prone IBS patients had more aborally propagated contractions in phase II and postprandially than the controls[37]. The contraction amplitude has, if anything, been shown to be increased in IBS patients with diarrhea[37] and reduced in those with constipation[35,42]. Our group has used high-resolution manometry in the small intestine with closely spaced recording points to evaluate the propagation pattern of individual pressure waves[43]. A study in IBS patients and healthy controls disclosed a higher proportion of duodenal individual pressure waves that propagated in a retrograde direction in IBS, especially in the postprandial phase. Moreover, when combining this high-resolution analysis with more conventional manometry analysis, abnormal findings were found in the majority of IBS patients[38].

Motility disturbances of the small bowel have also been demonstrated indirectly in transit studies, with rather uniform findings of accelerated transit through the small bowel in diarrhea predominant IBS[44,45] and delayed transit in constipation predominant IBS[18,44]. Small intestinal bacterial overgrowth (SIBO) is a condition caused by an abnormal number of bacteria in the small intestine, which is a common complication of severe small intestinal motor dysfunction[46,47]. Recently, provocative studies, using the lactulose hydrogen breath test[48], have proposed that SIBO is present in approximately 80% of IBS patients[49] and that this alteration responds favourably to antibiotic treatment with symptom improvement[50]. Moreover, the presence of SIBO in IBS patients has been proposed to be related to small intestinal motor abnormalities[51]. However, contradictory results exist and the relevance of SIBO in IBS is still open to debate[52-54].

To conclude, there is evidence of disturbed small bowel motility in IBS patients as a group, but no uniform motility pattern has been found and a consistent correlation between motility findings and symptoms has been difficult to demonstrate. Whether the observed motility abnormalities of the small intestine in IBS are due to factors related to the enteric or the central nervous system is not clear, but there is evidence to suggest that both may be true[35,39,55].

Colonic motility

Considerable effort has been made to find a specific abnormality in the myoelectrical and/or motor patterns of colon in IBS. However, a primary role for colonic dysmotility in the pathophysiology of IBS has been hard to demonstrate. Some of these difficulties may be explained by the fact that myoelectrical and motor events from the colon are less predictable and less well studied than corresponding events elsewhere in the gastrointestinal tract[56,57]. In the 1970s Snape and colleagues reported on

abnormal colonic myoelectrical activity in IBS (3 cycle/min pattern)[58,59], but subsequent studies failed to confirm this pattern to be specific for IBS[60,61]. Instead, since this pattern was demonstrated to be equally common among psychoneurotics without gastrointestinal symptoms it was suggested that this abnormality represented a colonic response to stress rather than being related to IBS[62]. Other techniques have focused on colonic spike patterns and demonstrated variations in the incidence of these[63], but whether these findings simply represent a non-specific response to diarrhea is not clear, since appropriate non-IBS controls have not been studied.

Several studies of basal colonic motility with intraluminal pressure recordings have not been able to demonstrate an abnormal pattern in IBS as compared to appropriate controls or differences between IBS patients with different symptomatology[17,64], but this has to some extent been contradicted in recent studies of colonic motility[65,66]. Some of the earlier studies were, however, able to detect frequent sigmoid contractions with high amplitude in association with pain reports from some of the IBS patients studied ("spastic colon"), although no group differences in rectosigmoid motility between IBS patients and controls could be detected[67]. Also, some recent studies have found an increased frequency of high-amplitude propagating contractions (HAPC) in the colon in non-constipated IBS patients[65,68,69], and more interestingly an association between pain episodes and HAPCs[65,70], possibly related to the presence of visceral hypersensitivity in IBS. Somewhat more consistent has been the finding that IBS patients seem to have an exaggerated and prolonged postprandial myoelectrical and motor response than healthy volunteers[17,65,71,72], even though negative studies also exist[66,73].

The normal motor response in the colon after nutrient administration is an increase in phasic motor activity and a progressive increase in tone as well[74]. At least two studies have failed to detect an abnormal colonic tone response after meal intake in IBS patients[66,75]. However, there are some recent data supporting altered gastrointestinal reflex activity in IBS patients, by demonstrating abnormal recto-sigmoid tone response following a low-caloric meal[76], or as an attenuated rectal tone response to colonic distension ("the colorectal tonic reflex")[77,78]. Hopefully these interesting studies will be followed by other investigations evaluating gastrointestinal reflex activity within the gastrointestinal tract, thereby providing new important information regarding neuromuscular function within the gastrointestinal tract in IBS patients. As in the small intestine motility alterations have also been demonstrated using transit studies. Transit through the colon influences the bowel habit of the patient[79,80], and differences exist in colon transit between IBS subgroups based on the predominant bowel habit[44,81].

To conclude, there is some evidence to suggest a disordered colonic motility in IBS, even though no uniform colonic motor pattern of this patient group is evident. Of great relevance to the symptomatology is probably the exaggerated colonic motor response to physiological stimuli such as food and, perhaps also stress and emotions in IBS[61,82], which together with an enhanced visceral sensitivity might be deleterious for these patients. Alterations in gastrointestinal reflex activity in IBS patients seem plausible, but follow-up studies are needed.

ABNORMAL GAS HANDLING

In patients with IBS complaints of "too much gas" causing abdominal pain and bloating is very common, and this has been proposed to be secondary to disordered intestinal motility in combination with an abnormal GI sensitivity, rather than caused by abnormal volume or composition of intestinal gas[83]. However, an abnormal colonic fermentation in IBS has been demonstrated in one study[84], but needs to be repeated by other groups. Of great interest, patients with IBS complaining of bloating has been found to have impaired transit of exogenous gas loads, and the following gas retention reproduced their symptoms[85]. Importantly, this abnormality can be modulated by nutrients[86, 87], physical activity[88] and body posture[89]. In follow-up studies using scintigraphy the small intestine seemed to be responsible for the ineffective gas propulsion in patients complaining of bloating[90], and altered gastrointestinal reflex activity in IBS patients might also be involved in the abnormal gas handling[91].

These findings tell us that IBS patients do not necessarily need to produce more gas in order to have gas related symptoms, but these may instead be due to motor dysfunction, resulting in a transport problem, and an enhanced visceral sensitivity.

ALTERED GASTROINTESTINAL SECRETION

Few studies have so far addressed GI secretion in IBS, partly due to methodological problems in assessing gastrointestinal secretion. However, there are some evidences supporting altered secretion in the small intestine of IBS. An old study demonstrated that patients with IBS have enhanced intestinal secretion in response to perfused bile acids in the ileum, relative to controls[92]. Our group has used potential difference measurements in the small intestine as an indirect measure of secretion in the small intestine[93], and in preliminary studies found an enhanced reactivity of the secretory component of the MMC in the small intestine in diarrhea-predominant IBS and to some extent also in constipation predominant IBS[94]. Ongoing studies will further evaluate the importance of secretory abnormalities in patients with IBS and the relevance for symptoms.

VISCERAL HYPERSENSITIVITY

Since James Ritchie in 1973 demonstrated colonic hyperalgesia by inflating balloons in the sigmoid colon in patients with "the irritable colon syndrome"[95] numerous reports on visceral hypersensitivity in IBS have appeared. Lowered perception thresholds for balloon distension in IBS patients have not only been demonstrated in the rectum[96] and colon[97], but also in the esophagus[98,99], stomach[100] and the small intestine[101,102]. These findings support a generalized enhancement of gastrointestinal sensitivity in IBS patients. However, a recent investigation has implicated that the hypersensitivity seems to be pan-intestinal for

those with multiple sites of their symptoms, whereas it was restricted to a specific organ in those with more localized symptoms[103]. Whether IBS patients have a general hypersensitivity remains debatable since divergent results exist regarding somatic sensitivity[104-106]. Patients with IBS also show an altered viscerosomatic referral pattern as another indicator of disturbed processing of viscerosensory information[107]. However, visceral perception is not abnormal in all patients with IBS[100,108] and there is a considerable overlap in colonic pain thresholds between IBS patients and healthy controls [109]. Moreover, the relationship to the symptom profile of the patient is controversial[108,110-112].

In an attempt to find a biological marker for IBS, Mertz et al evaluated different aspects of rectal perception in a group of IBS patients. They found that 94 percent of patients showed altered rectal perception in the form of lowered thresholds for aversive sensations (discomfort), increased intensity of sensations or altered viscerosomatic referral[96]. Also, a more recent study has come to the same conclusion and proposed that rectal sensitivity testing is useful to confirm the diagnosis of IBS and to discriminate IBS from other causes of abdominal pain[113]. The proposal that altered rectal perception is a biological marker for IBS has, however, been questioned and the importance of psychological factors in visceral perception has been stressed instead[114]. Psychological factors might certainly be of great importance in studies dealing with visceral sensations, and response bias[115] may influence results from balloon distension studies. A different conclusion can be drawn from a study by Corsetti *et al*, who showed that there was no difference between patients and healthy controls in identifying regular balloon inflations mixed with sham distensions, suggesting that the increased frequency of sensations often reported by IBS patients are not due to psychological response bias[116]. On the other hand, Whitehead and co-workers found that thresholds were correlated with psychological measures of anxiety and somatization[117]. However, in that study sexual abuse, reported to be associated with IBS[118], did not contribute significantly to the rectal pain sensitivity, which has been confirmed recently[119]. One explanation for these somewhat discrepant results may be that IBS patients demonstrate two different perceptual alterations: hypersensitivity to rectal distension, which is proposed to be largely due to peripheral alterations, and hypervigilance towards labeling a wide range of visceral stimuli in negatively affective terms, which is more related to psychological alterations[120].

A drawback with many of the studies assessing visceral perception in IBS is that they are made under fasting and non-stimulated conditions, under which patients normally do not report severe symptoms. However, it has been shown that repetitive sigmoid distensions - thought to imitate increased colonic motility after food intake[17], emotions[82] and stress[61] - resulted in hyperalgesia and increased viscerosomatic referral during rectal distensions in IBS patients. These findings were proposed to reflect a central sensitization of the dorsal horn neurons[121]. These data fit well with findings from studies evaluating the effects of rectal distension on spinal transmission of nociceptive signals, using a somatic cutaneomuscular flexion reflex (RIII reflex)[122], where IBS patients have an altered response[123]. Whether this is designated to changes in electrophysiological properties of the spinal nociceptive neurones or failure in the inhibition of nociceptive signals in spinal nerves is yet to be answered.

Patients with IBS often describe a correlation between their symptoms and stress, and they seem to be more susceptible to stressful events of daily life[124]. Using different methodologies, several studies now exist that demonstrate an altered visceral perceptual response in IBS patients relative to control subjects after and during stress[125-127], which might be of relevance for stress-related symptoms in IBS patients. Postprandial worsening of symptoms, as well as adverse reactions to one or more foods is common in IBS patients[128]. The effects of nutrients on colorectal sensitivity have been investigated in healthy volunteers and rectal sensitivity increases after nutrient ingestion[129]. Fat is also the main stimulus for this sensory component of the gastrocolonic response[130]. Recently we demonstrated enhancement of the colonic sensitivity in IBS patients after duodenal lipid administration as compared with healthy controls[75]. This finding has thereafter also been reproduced by other groups assessing the effect of duodenal lipid administration on rectal sensory function[131,132], making it fair to state that patients with IBS seem to have an exaggerated sensory component of the gastrocolonic response.

Visceral hypersensitivity may also be affected by motor characteristics and biomechanical properties of the gut, but studies assessing for instance rectal compliance have come to somewhat inconclusive results[108,133,134]. Moreover, a study using impedance planimetry found no clear evidence of altered biomechanical properties in the rectum in patients with IBS and hypersensitivity[135]. However, more studies assessing the relationship between sensory and motor characteristics and biomechanical properties of the gastrointestinal tract in IBS patients are needed.

To conclude, visceral hypersensitivity is currently considered to be perhaps the most important pathophysiological factor in IBS. Importantly, several external and internal factors can modulate visceral sensitivity. The link between visceral hypersensitivity and specific symptoms in IBS deserves further studies.

DYSREGULATION OF THE BRAIN-GUT AXIS

The brain-gut axis is a model describing bidirectional pathways linking emotional and cognitive centres in the brain with visceral afferent sensation and intestinal function. Several observations have led to the hypothesis of a dysfunctional brain-gut axis in the pathophysiology of IBS[136-138]. Brain imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have been used to investigate brain response during visceral stimulation with rectal distensions. Despite contradicting results, several studies indicate differences between IBS patients and healthy controls in activation of different pain processing regions such as the anterior cingulate cortex (ACC), thalamus, insula and prefrontal cortex (PFC)[139].

Using PET, Silverman et al initially reported that painful rectal distension in IBS patients resulted in reduced

ACC activity but enhanced activity in the PFC during anticipation of rectal pain suggesting a hypervigilance towards the stimulation and a failure to activate endogenous pain inhibition systems[140]. However, Mertz et al later published an fMRI study showing increased activity in the ACC indicating a normal activation pattern but a heightened sensitivity of the brain-gut axis[141]. Several brain imaging studies have been published thereafter with somewhat divergent results, with reports of increased activity in the insula, PFC and thalamus[142,143], as well as in the cingular cortex[142,144,145], but also decreased activity in the insula, amygdala and striatum[146]. The discrepancies in results are probably explained by factors such as small study populations and pooling of results from heterogeneous groups, as well as the use of different methodologies[147]. It has for instance been demonstrated that male and female IBS patients show differences in activation of brain regions[148,149], just like the activation pattern differs between IBS subgroups based on the predominant bowel habit[150]. The psychological state of the patient is also important since emotional status has been shown to modulate brain activation patterns[151]. Interestingly, changes in some brain regions have also been associated with treatment response in IBS[152]. In addition to brain imaging, IBS patients have also shown different results than healthy controls in studies using electroencephalography (EEG)[153,154] and evoked potentials[155,156].

Central nervous system communication with the gut is mediated through the parasympathetic and sympathetic pathways of the autonomic nervous system (ANS) by modulation of the enteric nervous system. Several studies have reported autonomic dysfunction in IBS[157-161]. The results are inconsistent, but increased sympathetic and decreased parasympathetic activity in IBS patients compared with healthy controls are the most frequently reported differences[162-166]. Again, the contradictory results may partly be due to varying experimental designs with differences in study populations. Anxiety and depression influences autonomic function in IBS[167], and there also seem to be discrepancies between different subgroups of IBS patients[162,165,168]. Recently Tillisch *et al* also showed gender differences in ANS response to visceral stimulus, with more prominent alterations in male IBS patients[169].

Another important system in the communication between the brain and the gut is the hypothalamic-pituitary-adrenal (HPA) axis, with important effects on GI motility, sensation and immune function[170]. Activation of this system takes place in response to both physical and psychological stressors[171]. Since patients with IBS often report stress-related symptoms[124], it has been a logical step to evaluate the HPA axis and its effect on GI function in IBS. Also here results are divergent with investigations reporting attenuated[172], normal[125] and enhanced reactivity[127,173] of the HPA-axis in IBS patients in response to various stressors. Again, different study designs, patient characteristics and other factors might be the explanation for the somewhat heterogeneous results[174].

To conclude, there appears to be alterations along the brain-gut axis and in autonomic nervous function in patients with IBS. However, there are discrepancies between existing studies, and in future studies standardization of the methodology, as well as strict inclusion criteria and evaluation of larger patient groups will enhance our understanding of the interaction between the gut and different parts of our nervous system.

CONCLUSION

The pathophysiology of IBS is complex and still incompletely known. Both central and peripheral factors, including psychosocial factors, abnormal GI motility and secretion, and visceral hypersensitivity, are thought to contribute to the symptoms of IBS. However, in order to be able to find new treatment alternatives for this big patients group more knowledge about the pathophysiology of IBS is needed.

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