in Japan) in terms of H_1ROs. The results showed that the H_1ROs of both drugs were 26 and 0%, respectively (Tashiro et al., 2004). The H_1RO of 26% (mean value for the whole brain) was relatively high for a mildly-sedative antihistamine, suggesting that cetirizine might show dose-related brain penetration. This has been the rationale for conducting the present study in order to investigate whether dose-related BBB penetration is present or not. Examining the dose dependency of mildly-sedative antihistamines is also of great social importance because of overcompliance as mentioned in the introduction section. Comparison of H_1ROs following the oral administration of cetirizine 10 and 20 mg indicated clear dose-dependency in H_1ROs (Table 1 and Figure 2), although the difference was not statistically significant (Figure 2).

Variation in the BBB permeability among different antihistamines can be explained by various factors such as lipophilicity, molecular size, and different actions of drug transporters including a P-glycoprotein (P-gp). This is an efflux pump expressed in capillary endothelial cells in the BBB (Tashiro et al., 2006). Many sedative antihistamines are often lipophilic and can be absorbed in full amount in the gut, and they can freely diffuse into the brain space. In the case of mildly-sedative antihistamines with reduced lipophilicity, both gut absorption and brain penetration are limited. For fexofenadine, a substrate of P-gp, both gut absorption and BBB permeability are highly reduced because of its low membrane permeability and high action of P-gp. For cetirizine, also a substrate of P-gp but probably to a lesser extent than fexofenadine, will allow a certain amount of BBB penetration (Chen et al., 2003; Molimard et al., 2004). Our recent study demonstrated that bepotastine 10 mg, a new mildly-sedative antihistamine produced in Japan, has a similar structure to that of cetirizine and its H_1RO is similar to that of cetirizine 10 mg (mean value of frontal and cingulate: cortices,12.1%) (Tashiro et al., 2008). It is interesting to mention that bepotastine's chemical structure resembles that of cetirizine and its membrane permeability is greater than that of fexofenadine (Ohashi et al., 2006).

In our previous healthy volunteer study ($n = 10$)(Tashiro et al., 2004), the plasma concentrations of hydroxyzine and cetirizine (a main metabolite) following oral administration (120 min post-administration) of hydroxyzine 30 mg was 20.0 +/− 9.3 ng/ml and 146.3 +/− 50.3 ng/ml, respectively, although these results were not presented in the paper. In addition, the plasma cetirizine concentration following cetirizine treatment (20 mg) was 489.0 +/− 118.8 ng/ml. These pharmaco-kinetic data may suggest that a large proportion of hydroxyzine molecules rapidly distributed from the plasma into the tissue compartment and relatively small part of hydroxyzine molecules is rapidly metabolized into cetirizine. And according to Simons and colleagues, the elimination half lives do not differ largely between hydroxyzine (29.3 +/− 10.1 h) and cetirizine (24.8 +/− 7.7 h)(Simons et al., 2008). It seems that the subjective sedation is not associated with the plasma cetirizine concentration, but is associated with the brain distribution (penetration) of hydroxyzine measured as H_1RO.

Interestingly, a significant correlation between H_1RO and subjective sleepiness was observed following treatment with hydroxyzine 30 mg, but not following the treatment with cetirizine (Figure 3). This result suggests that subjective sleepiness is not reliable for evaluating the level of sedation particularly for mildly-sedative antihistamines. Thus, measurement of H_1RO using PET seems to be promising as recommended by the consensus group on new generation antihistamines (CONGA) (Holgate et al., 2003). CONGA is responsible for summarizing the core measures regarding the evaluation of the sedative profiles of new generation antihistamines (Holgate et al., 2003).

Here, we should discuss the limitations of the present study. First, we did not find a good correlation between subjective sleepiness and H_1RO. This would be partly because of inter-individual differences in drug responses. Considering variation in the results of previous cognitive studies on cetirizine (Gengo and Gabos, 1987; Gengo et al., 1990; Ramaekers et al., 1992; Bonifazi et al., 1995; Vermeeren et al., 2002), cetirizine is possibly an agent with relatively large inter-individual difference in its sedation. For the future replication to evaluate dose dependency, it would be better to scan each subject under three conditions of CET10, 20 mg and placebo using the same PET scanner. Different scanners were used for different antihistamines in the present study, though both scans were respectively compared to the placebo data obtained by the same scanner. In the second point, we did not measure the plasma drug concentration and were not able to examine the direct relationship between plasma drug concentration and H_1RO. Future study should clarify this relationship as well.

In conclusion, we examined the H_1RO of cetirizine at different oral doses of 10 and 20 mg, and compared the results with those from the oral administration of hydroxyzine 30 mg. Cetirizine 10 mg occupied

approximately 13% of available H_1Rs in the frontal brain (frontal and cingulate cortices), while cetirizine 20 mg occupied approximately 25% of H_1Rs, confirming that brain penetration of mildly-sedative antihistamines tends to be dose-dependent. In addition, it is noteworthy for users to know that oral administration of cetirizine 10 mg could be more safely used for the treatment of allergic disorders, while an increased dose (20 mg or more) could result in mild sedation.

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Chapter IV

Is Colonic Hypersensitivity Really a Biological Marker of Irritable Bowel Syndrome (IBS)? -A Role of Visceral Sensitivity on Pathophysiology of IBS.

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Introduction

Irritable bowel syndrome (IBS) is common and has a great impact on quality of life of the patients and medical/social economy [1], yet the mechanisms by which symptoms arise are poorly understood. Chronic and/or recurrent abdominal pain/discomfort associated with abnormal bowel habits is a main symptom of IBS [1, 2]. Current Rome III diagnostic criteria for functional gastrointestinal disorders are based on only clinical GI symptoms and symptom frequency [3]. Although abnormal gastrointestinal motility has been considered to be strongly associated with major symptoms of IBS for years, recent studies revealed some disappointing findings in terms of purely motility disorders [4]. Currently, visceral hypersensitivity is the leading hypothesis to explain the major pathophysiology of IBS and other functional gastrointestinal disorders [5].

In 1973, Ritchie [6] first reported that IBS patients showed more sensitive to intraluminal balloon distention of the colon than normal subjects. A barostat technique, in which operating pressure and volume in the bag inserted in the gut are controlled and recorded by a computer

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via an air inflation device, was developed approximately two decades ago [7, 8] and is widely used to determine visceral hypersensitivity for now. Using this technique, Whitehead et al. [7], Mertz et al. [9] and others [10] confirmed that majority of IBS patients have lower pain thresholds in response to colonic or rectal distention. Mertz et al. [9] proposed that altered visceral perception in the rectum is a biological marker of patients with IBS. Underlying visceral hypersensitivity in most of IBS patients was observed as allodynia (decreased nociceptive threshold) and/or hyperalgesia (increased nociceptive response). Bouin et al. [11] found that pain threshold to the rectal distention was highly specific inferior to 28 mmHg and was rare superior to 40 mmHg. Furthermore, recent studies [12, 13] using a barostat technique demonstrated that there was no difference in pain perception threshold to intraluminal distention between subtypes of bowel movement in IBS patients.

However, little is known about precise mechanism of visceral hypersensitivity and relationships between clinical symptoms and visceral sensitivity in patients with IBS. In the current article, possible mechanisms of abnormal visceral perception in IBS are discussed, focusing on the brain-gut interaction.

Possible Mechanism of Visceral Hypersensitivity in IBS

Visceral sensory signals are transmitted from the gut via afferent nerve fibers traveling through the spinal cord to the brain. Brain response to some stimulus in the peripheral organs is measured by several imaging techniques (e.g. positron emission tomography, PET or functional magnetic resonance imaging, fMRI). Human brain imaging studies suggested that IBS patients may have altered central activations (e.g. anterior cingulate cortex, ACC) during painful rectal distention compared with healthy subjects [14-17]. The enhanced central response could be caused by an increased signal and/or the signal amplification from the gut to the brain via the spinal cord and brainstem. In addition, disturbance in the descending pain inhibitory system on the brain-gut link could give rise to visceral hypersensitivity.

Patients with IBS showed more enhanced perception in the gut to psychological or physiological stress condition [18] or attention/hypervigilance itself to the aversive stimulus [19]. Anticipation to rectal painful distention alone enhanced the similar brain areas with response to actual rectal stimulation [20]. On the contrary, placebo administration [21] or distraction to aversive stimulus [22] could cause decrease in visceral perception.

On the other hand, previous findings on the modulation of pain sensitivity in the colon support some mechanisms of peripheral sensitization in IBS: (1) An abnormal colo-colic reflex in the forms of exaggerated motility was demonstrated after repetitive nonpainful distentions of the sigmoid colon in patients with IBS [23]; (2) rectal administration of lidocine in IBS patients decreased rectal sensitivity to intraluminal distention [24]; (3) glycerol instilled into the rectum induced visceral hypersensitivity [25]; and (4) low grade inflammation of intestinal mucosa has been verified by several studies of IBS [26]. Evidence for the hypothesis of the peripheral sensitization is seen in patients with postinfectious IBS (PI-IBS) who give a preceeding history of acute GI infection prior to the onset of their IBS symptoms [27]. Barbara et al. [28] have shown that increased mast cells have been observed

in the colonic mucosa in PI-IBS patients and that close proximity of mast cell and nerves in the colon was correlated with severity of abdominal pain. Gecse et al. [29] reported that mucosal application of fecal supernatants from IBS patients with diarrhea evoked colonic hypersensitivity in mice, which effect was associated with serine protease activity mediated through protease-activated receptor 2 (PAR-2). PAR-2 is expressed by nociceptive neurons and activated during inflammation by proteases from mast cells, the intestinal lumen, and the circulation.

Interestingly, peripheral administration of corticotrophin-releasing hormone (CRH), which activates the hypothalamic-pituitary-adrenal axis and is considered to be a major mediator of stress responses, induced rectal hypersensitivity after repetitive painful rectal distention in animal models [30] and humans [31]. On the other hand, peripheral administration of α -helical CRH, a non-selective CRH receptor antagonist, resulted in reduction of enhanced visceral pain perception as well as negative mood in response to gut stimulation in patients with IBS [32]. These findings indicate that both central and peripheral modulation may contribute to abnormal visceral perception in IBS. Thus, visceral hypersensitivity observed in IBS patients may be heterogeneous pathophysiological findings.

Relationships between Visceral Hypersensitivity and Clinical IBS Symptoms

No consensus has been established so far on relationships between visceral perception and symptom severity in patients with IBS although visceral hypersensitivity has been considered to be one of major pathophysiology for IBS. Drossman et al. [33] reported that IBS severity was weekly correlated with visceral hypersensitivity to rectal balloon distention. In a recent study [34], a multivariate analysis revealed that abdominal pain and bloating severity were independently associated with altered rectal perception observed in patients with IBS. In contrast, Lembo et al. [35] reported that IBS severity did not predict the development of rectal hypersensitivity to repetitive sigmoid distention. Moreover, no significant correlation was found between rectal threshold and either IBS symptom intensity in another study [36]. Likewise in children with IBS and functional abdominal pain (FAP), rectal hypersensitivity was not associated with severity of GI symptoms [37], suggesting that IBS symptom severity might be more influenced by other factors in childhood.

With respect to another site of the large intestine, the descending colon, our research group confirmed that pain threshold to intraluminal distention was significantly correlated with abdominal pain or overall symptom severity in patients with IBS despite subtypes of bowel habit [13]. Interestingly, we also found that abdominal pain severity was positively correlated with colonic motility in IBS patients with diarrhea (IBS-D) alone [13]. On the other hand, abdominal bloating severity was negatively correlated with colonic motility in IBS with constipation (IBS-C) alone [13].

These results suggest that not only visceral hypersensitivity but also other factors such as altered GI motility and psychological abnormality might be more or less associated with development of IBS symptoms.

Future directions

Novel therapeutic approaches for abnormal visceral sensitivity in IBS have been investigated in both basic and clinical settings (Table 1) [38]. Treatment with interpersonal psychotherapy [39] or serotonin selective reuptake inhibitor (SSRI) antidepressants [40] failed to change in rectal pain threshold to balloon distention despite clinical improvement in patients with IBS. However, it has been reported that kappa agonist fedotozine [41] or melatonin [42] relieved pain hypersensitivity to colonic distention in patients with IBS. Delvaux et al. [43] reported that 5-HT_3 antagonist alosetron also increased rectal pain threshold in IBS-D patients. During treatment with a tricyclic antidepressant, amitriptyline in patients with IBS-D, not only clinical symptoms improved but also rectal pain threshold significantly increased [44]. Furthermore, Lea et al. [45] found that gut-focusing hypnotherapy normalized visceral sensitivity with improvement of GI and psychological symptoms in patients with IBS. Overall, these findings indicated that visceral sensitivity observed in IBS can be manipulated by pharmacological or psychological intervention. Future clinical trials are awaited to determine whether changes in visceral sensitivity would be considered as one of reliable biological markers for improvement of IBS symptoms.

In conclusion, visceral hypersensitivity is one of most frequent findings and may play a major role in development of symptoms in patients with IBS. The implication of this idea is that it may be advantageous to target pain sensitivity for treatment of IBS. Further studies are needed to clarify the precise mechanism of visceral pain modulation in the brain-gut link.

Table 1. Novel candidate therapeutic agents for visceral hypersensitivity in IBS.

Opiates
κ1-opioids
μ-opioids
Serotonergic and adrenergic receptor modulators
5-HT_3 receptor antagonists
5-HT_4 receptor agonists
a_2-adrenergic receptor agonists
Antidepressants
Tricyclics
Selective serotonergic reuptake inhibitors
Serotonin and noradrenalin reuptake inhibitors
Neuropeptide receptor modulators
Neurokinin 3 receptor antagonists
CRH1 receptor antagonists
Others
Somatostatin analogue
Cholocystokinin (CCK)-1 antagonists
Melatonin

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Central Serotonin Neurotransmission Disorders Correlate with Visceral Perception and Psychological Characteristics in Patients with Functional Dyspepsia

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Background & Aims: Visceral perception of functional dyspepsia (FD) is based on the brain-gut interaction via various neurotransmission pathways. Peripheral or central serotonergic abnormalities are associated with the pathophysiology of functional gastrointestinal disorders or psychiatric depression and anxiety. To examine the roles of the cerebral serotonin (5-HT) neurotransmission systems in visceral perception of FD patients, we examined both 5-HT transporter (5-HTT) binding potential in the brain and the correlation between differences between patients and controls in 5-HTT binding potential and abdominal symptoms. **Methods:** Patients with FD diagnosed according to the Rome III criteria (N=9, female: 6, age range 25-61 yrs) were recruited for this study. There were 9 healthy controls (female: 3, age range 36-76 yrs). To measure 5-HTT binding potential with region-of-interest data in areas of the thalamus, putamen, caudate, amygdala, midbrain, and cerebellum (as a reference region), positron emission tomography (PET) with [^{11}C]N,N-dimethyl-2-(2-amino-4-cyanophenylthio) benzylamine ([^{11}C]DASB), which binds specifically to 5-HTT, was performed. We used the Multi-linear Reference Tissue Mode method within the standard software package of PMOD Technologies for analysis of [^{11}C]DASB with reference to the co-registered MRI images. Clinical symptoms were evaluated on the Gastrointestinal Symptoms Rating Scale (GSRS) including subscales for abdominal pain and indigestion. Depression and anxiety were evaluated on the Self-Rating Depression Scale and the State-Trait Anxiety Inventory. **Results:** All scores for abdominal pain, indigestion, depression, and anxiety were higher for FD patients than for controls ($p<0.01$). In FD patients, the binding potential of [^{11}C]DASB in the midbrain ($p=0.001$) and amygdala ($p=0.065$) was higher than in the corresponding areas in controls, while there were no differences between the groups in the thalamus, putamen, or caudate. Binding potential of [^{11}C]DASB in the midbrain was correlated with total GSRS ($p=0.018$, $r=0.572$), indigestion ($p=0.021$, $r=0.565$), and abdominal pain ($p=0.091$, $r=0.420$) scores, while in the amygdala it was correlated with total GSRS ($p=0.080$, $r=0.426$), indigestion ($p=0.057$, $r=0.469$), depression ($p=0.091$, $r=0.413$), and anxiety ($p=0.096$, $r=0.406$) scores. **Conclusion:** These findings suggest that in FD patients there are disorders of central 5-HT neurotransmission, especially in the midbrain and amygdala, which are correlated with their visceral symptoms and psychological characteristics.

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Evidence for Altered Central Noradrenergic Modulation in Irritable Bowel Syndrome (IBS)

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Background: The importance of central noradrenergic functions in IBS has been implicated, but has not been directly assessed. **Aims:** To study the effect of pharmacologic modulation of central noradrenergic activity on brain responses and associated subjective responses in IBS and compare to healthy control subjecs (Ctrls). **Methods:** In a double-blind study, 11 IBS patients (6 men) and 11 Ctrls were studied 3 times, with an auditory vigilance task after ingestion of the α2 adreno receptor (α2AR) antagonist yohimbine (YOH; increases presynaptic NE release), the α2AR agonist clonidine (CLO; reduces NE release via presynaptic α2AR and blocks postsynaptic α2AR) or placebo. Plasma norepinephrine (NE), blood pressure, self-rated mood, and [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET) images of cerebral glucose metabolism, which served as an index of relative regional brain activity, were acquired. **Results:** IBS patients had significantly higher plasma NE levels (all $p<0.05$) than Ctrls both before and after ingesting all three drugs. Both noradrenergic drugs produced expected effects on plasma NE, blood pressure, mood and brain activity. YOH increased anxiety and plasma NE more in IBS patients than Ctrls, and the increases were correlated with each other ($r=.63$). Connectivity analyses indicated a functional circuit in dorsal brainstem including locus coeruleus (LCC), amygdala and infragenual anterior cingulate cortex (iACC). YOH-mediated *reduction* of activity in this arousal network was stronger in all three regions of Ctrls (consistent with reduced presynaptic α2AR-mediated in IBS), whereas clonidine-mediated *increased* activity was stronger in the iACC and amygdala of IBS patients (consistent with greater noradrenergic tone). In Ctrls, but not IBS patients, activation of amygdala and iACC were inversely correlated with activation of the rostral ACC, and anxiety covaried directly with activity in limbic and right frontotemporal cortices, but indirectly with activity in left frontotemporal cortex. The latter finding is consistent with expected relationships between anxiety and the frontal laterality of brain activity in Ctrls, but not IBS patients. **Conclusions:** IBS patients had reduced responsiveness or downregulation of presynaptic inhibitory α2ARs as compared to Ctrls, resulting in increased plasma levels of NE and increased noradrenergic tone within central arousal circuits (amgydala, iACC, LCC). Activity in these circuits, which is correlated with anxiety, is biased toward greater adrenergic excitability and/or reduced descending inhibition from rostral cingulate and prefrontal cortices in IBS.

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Evidence for Altered Brain Circuits Underlying Selective Attention to Negative Emotional Stimuli in IBS

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BACKGROUND: Hypervigilance and attentional bias towards visceral sensation has been implicated in central pain amplification in IBS. AIM: To identify the neurobiological substrate mediating attention bias between IBS and healthy controls (Ctrls). METHODS: Brain activity in 23 female Rome+ IBS patients and 15 healthy women controls was studied using a Siemens Allegra 3T MRI scanner, using validated emotional reactivity (Emotional Matching vs. Forms Matching) and modulation (Emotional Labeling vs. Gender Labeling) paradigms that involve the viewing and labeling of negatively valenced emotional faces to activate brain circuits involved in emotion processing and arousal. Reaction Time (RT) was measured via Superlab presentation software. Paired group t-tests and a contrast analysis using a random effects general linear model were applied to test for difference in reaction time due to the interaction of group and condition. SPM5 was used to assess the relationship between reaction time and the brain activity and to test for group differences in these correlations using a false discovery rate of 5%. RESULTS: Both IBS and Ctrls showed significantly slowed responses during emotion matching and emotion labeling tasks compared to the respective control tasks ($p's<.001$). There was an observable trend for IBS patients to have slower RTs during all conditions, however, these differences only achieved statistical significance during emotion matching and labeling ($p's<.01$). Across all tasks, group differences were observed in the relationship between the RT and the medial prefrontal cortex (mPFC)/rostral anterior cingulate cortex (rACC), subgenual ACC, dorsal and lateral PFC, hippocampus, and dorsal pons. Examining the within group correlation with RTs revealed that IBS patients had more robust correlations whereas no regions could be considered significantly correlated in Ctrls. Further exploring these results by extracting the correlations (betas) from the representative mPFC voxel using the VOI toolbox in SPM revealed a moderately strong negative correlation between RT and mPFC/rACC for IBS ($r=-.38$, $p<.001$) but not for Ctrls ($r=-.07$, $p=.56$). CONCLUSIONS: IBS patients demonstrated selective attention biases primarily towards negative emotional stimuli in comparison to Ctrls. The group differences observed in the correlation between RT and PFC regions and the inverse correlation of RT and mPFC in IBS subjects, suggests that slower RTs in IBS are associated with reduced engagement of a PFC region involved in corticolimbic inhibition.

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Impact of Serotonin-3 Receptor Gene Polymorphism On Brain Activation By Rectal Distention in Human

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Background & Aims: Serotonin (5-HT)-related genes are the candidates that regulate the reactivity to stimulus in irritable bowel syndrome (IBS). The 5-HT3 receptor antagonists are used for the treatment of IBS. We previously reported that C allele of the 5-HT3B gene (HTR3B) polymorphism rs1176744 is more common in IBS population (Gastroenterology 132: A134-5, 2007). This variant dramatically augments the signaling of the 5-HT3 receptor (Proc Natl Acad Sci U S A 105: 722-7, 2008). We tested our hypothesis that C allele of HTR3B differentially activates regional brain to the rectal distention in human. Methods: Twenty-eight subjects without any organic disorders participated in this study. This study was approved by the Ethics Committee and all subjects gave the written informed consent. DNA was extracted from the peripheral blood. Using polymerase chain reaction, genotype of HTR3B was determined. Individuals with A/A genotype (n = 14) and individuals with C allele (genotype A/C and C/C, n = 14) were compared. Barostat bag was inserted to the rectum. The bag was intermittently inflated with no (0 mmHg) or intense (40 mmHg) stimulation with random order. Radioactive H2[15-O] saline was injected at the bag inflation and positron emission tomography was performed. Changes in rCBF were analyzed using statistical parametric mapping 2. Results: Intense rectal distention induced significant activation in the thalamus, insula, anterior cingulate cortex, and precuneus in both A/A subjects and A/C + C/C subjects ($p < 0.0001$). Subtraction analysis (image at 40 mmHg - image at 0 mmHg) differentiated activation pattern between the genotypes. A/C + C/C subjects showed significantly more activation in the right amygdala, left insula ($p < 0.0001$), and left orbitofrontal cortex (BA11, $p = 0.0001$) than A/A subjects. Conversely, AA subjects showed significantly more activation in the right dorsolateral prefrontal cortex (BA9) and right precuneus ($p < 0.0001$) than A/C + C/C subjects. Conclusion: These data suggest that individuals with 5-HT3 receptor gene polymorphism presumably with enhanced function respond to the gut-derived signal more in the brain regions of negative emotion, body recognition, and discrimination of the stimulus value. HTR3B polymorphism may partially predict the individual effects of 5-HT3 receptor antagonists in IBS.

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Neural Correlates of Sensory & Affective Pain Dimensions in Functional Dyspepsia: A $H_2{}^{15}O$-PET Study

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Background The lateral (somatosensory cortex, SI/SII) & medial pain system (anterior cingulate cortex) are the neural correlates of the sensory-discriminative & affective-motivational pain dimension, respectively. However, these findings are based almost exclusively on the somatic pain literature. ***Aim*** To study the neural correlates of sensory & affective pain dimensions in Functional Dyspepsia (FD). ***Methods*** Brain $H_2{}^{15}O$-PET was performed in 25 FD patients during 3 conditions: no distension (baseline), distension at discomfort threshold & sham. Sensory & affective pain dimensions were measured using Visual Analog Scales (VAS, range 0-150). Data were analyzed in SPM2 with threshold $p_{uncorr}<.001$. Sensory & affective VAS scores were correlated with mean brain activity during baseline, distension & sham and with contrasts distension>baseline & sham>baseline. ***Results*** *Behavioural* Mean sensory & affective VAS scores were 107±46 & 120±26, respectively. *Imaging* results are summarized in the table. Sensory pain scores correlate with activation in the lateral pain system, but also with regions reported to be involved in affective (hippocampus, cingulate subregions, orbitofrontal cortex), cognitive (cingulate, dorsolateral prefrontal) and modulatory (cingulate, dorsomedial prefrontal) aspects of pain in the somatic pain literature. Affective pain scores correlate with activation in only a few regions, some of which have been reported to be involved in affective pain dimensions (lateral orbitofrontal cortex, anterior cingulate cortex). ***Conclusion*** In FD, mainly sensory pain scores correlate with brain activation in several regions, including the lateral pain system but also affective and cognitive areas.

were: "made to have intercourse/oral/anal sex against will" (46.6%), "fondled under force/threat" (41.8%) and "having seen/handled dead bodies not in a funeral" (40.4%). The TQ also identified high prevalence of traumas (e.g., sex against will because of physical force/threat (49.4%), sexual harassment (65.1%) and domestic violence (48.2%)), with many reporting occurrence during military service (41.5%, 64.8% and 60.0% respectively). Almost 34% also reported history of childhood sexual abuse. Overall, IBS cases were significantly more likely to experience 9 of 18 THQ traumas, with another 4 closely approaching significance. Excess IBS risk conveyed by selected traumas was modestly increased in age- and ethnicity-adjusted model, with 11 traumas conveying significant risk (OR=1.72 - 2.43). Women veterans with IBS were also more likely than those without IBS to have PTSD (22.1% vs. 10.7%, p<0.006) and depression (44.2% vs. 30.0%, p=0.01). However, the excess IBS risk was only slightly attenuated after adjusting for these risk factors. Conclusion- A high prevalence of IBS, PTSD, and trauma was observed among women veterans. The most commonly reported traumas were sexual, with 49.4% of all women veterans reporting being forced to have sex during their military service. A history of many traumas was associated with an approximately 2-fold increased IBS risk. However, neither PTSD nor depression seems to explain this association.

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The Effects of *Bifidobacterium breve* On Gastrointestinal Symptoms, Cytokines, Fecal Microbiota and Organic Acids in Irritable Bowel Syndrome

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Background: Earlier studies support probiotics as the useful agent for treating patients with irritable bowel syndrome (IBS) but simultaneous changes in intraluminal environment, cytokines, and symptoms by probiotics are unknown. We tested our hypothesis that the above factors are simultaneously improved by Bifidobacterium breve. Methods: Subjects were 54 Rome II-defined IBS patients. IBS subtypes (constipation: C, diarrhea: D, and mixed: M) were classified with Rome III. Subjects were randomized to receive Bifidobacterium breve Yakult (n=27, 11 men, 16 women, C6/D10/M11) or placebo (n=27, 11 men, 16 women, C9/D8/M10) for 8 weeks. Primary endpoint was IBS symptoms assessed with Self-reported IBS Questionnaire (SIBSQ). Secondary endpoints were quality of life (QOL) and negative emotion. Stool sampling for analysis of intestinal microbiota and organic acids, blood sampling for measuring cytokines (tumor necrosis factor-alpha, transforming growth factor-beta), and abdominal X-ray film for analyzing bowel gas volume were performed before and at after the treatment. Results: Composite score for abdominal pain, discomfort, and loose stool of SIBSQ in B. breve group significantly improved compared with that in placebo group (ANOVA: period effect; p<0.0001, group x period interaction; p=0.036). ANOVA of TNF-alpha also showed significant group x period interaction (p=0.015). The 15 bacterial counts and levels of 8 organic acids (acetic, succinic, valeric, iso-valeric, formic, butyric, propionic, and lactic acids) were not changed by administration of B. breve. However, significant correlation between changes (before and after the treatment) in SIBSQ score and changes in acetic acid was detected in placebo (r=0.382, p=0.05) but not in B. breve. Conclusion: These data suggest that administration of B. breve to IBS alleviates GI symptoms simultaneously with improved level of TNF-alpha. Fecal acetic acid as the product of microbiota is likely to influence on IBS symptoms in the natural course but not in the administered state with probiotics.

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Implementation of National Dyspepsia Guidelines to Reduce Prescribing and Return Patients to Self Care: Results from An Educational Intervention and Prospective Clinical Audit in England

Mark Connolly, Aomesh Bhatt

Background: Clinical guidelines from the UK National Institute for Health and Clinical Excellence (NICE) for the Management of dyspepsia in adults in primary care suggest the need for an annual review of patients requiring long-term management of dyspepsia with the aim of stepping down (S-D) or stepping off (S-O) treatment, and returning patients to self care for breakthrough events. Aim: To evaluate the long-term effectiveness of an educational strategy aligned with NICE clinical guidance of S-D or S-O treatment and encouraging patients to return to self care. The results described here are the long-term follow-up from an earlier educational intervention study. Method: We report findings from 2.5 years follow-up based on a subset of patients who had successfully been S-D or S-D long term proton-pump inhibitors (PPI) treatment by a nurse led educational strategy which followed NICE guidelines (2004). The original audit published elsewhere, (Evans N.,BJHCM 2007;13:425-430), was a prospective multi-centre audit that recruited patients with non-ulcer dyspepsia (NUD) and Gastro-oesophageal reflux disease (GORD) treated with PPI for >2 months from nine primary care practices in a suburb of London. Patients were offered a treatment change to low-dose PPI (step down) plus alginate or alginate (Gaviscon Advance) alone (step off). Exclusion criteria were *H. pylori* infection, duodenal or gastric ulcer and complicated dyspepsia. Results: The mean age of participants at baseline was 64 (SD 13.5), 49% male and 93% receiving PPI for >6 months with no difference between S-D and S-O groups. Of the eligible patients 40% (n=112) and 28% (n=77) agreed to S-D and S-O therapy, respectively, of which 93% (n=104) were successfully stepped down to low-dose PPI plus alginate and 78% (n=60) stepped off onto alginate alone. At 2.5 years following the educational intervention 81% (n=153) of patients who had successfully completed the initial step down/step off programme had retained their status. With respect to S-D and S-O therapy recommendations 88% (n=92) and 66% (n=40) of subjects maintained the alternative therapy option at 2.5 years, respectively. Conclusions: The results indicate that in appropriate patients, educational interventions are effective for reducing long term PPI prescribing. A higher proportion of subjects stepping down maintained the recommended therapy. The results highlight that reducing unnecessary long term use of PPIs and enabling patients to return to self care with alginates is unlikely to compromise symptom control in patients with reflux disease and is also likely to offer valuable cost-savings.

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Impact of Baseline Severity On the Performance of IBS Clinical Trial Endpoints: Results of the ROME Foundation Endpoints Working Group Meta-Analysis

Brennan M. Spiegel, Roger E. Bolus, Michael Camilleri

Background: It remains unclear how best to measure patient reported outcomes (PROs) in IBS. The performance of binary PROs (*e.g.* "adequate relief") as trial endpoints may be influenced by baseline symptom severity. An alternative is to measure improvement on a linear severity scale, and to define "response" over time of treatment as ≥50% improvement. **Aim:** To perform a meta-analysis of clinical trials to measure the impact of baseline pain severity on binary endpoints vs. the 50% improvement criterion. **Methods:** We pooled patient-level data from 4 pharmaceutical companies comprising 12 previously conducted IBS trials involving 10,066 participants. In addition to demographics and symptom profiles, each study included a baseline and end-of-study measure of abdominal pain, and an end-of-study binary global endpoint. We adopted pain intensity as a surrogate for severity, and created a harmonized modified T-scale for "pain severity" (mean=100; SD=10) spanning all trials. We trichotomized patients into baseline severity tertiles (mild, moderate, severe), and compared response rates across tertiles for the 2 endpoints (binary vs. ≥50% improvement) using chi-squared. We performed multivariate logistic regression to measure the effect of baseline severity on responses while adjusting for IBS sub-type, treatment status, age, sex, and IBS duration. We used an *a priori* criterion to define minimal clinically important difference, defined as a difference ≥5 points on the pain severity T-scale (*i.e.* effect size ≥0.5) in responders *vs.* non-responders. **Results:** There were 9044 evaluable subjects (mean age= 44; 85% F; 58% IBS-C; 31% IBS-D). Using the binary endpoint, the proportion responding in the mild, moderate, and severe groups was 42.2%, 40%, and 38.2%, respectively (p= 0.0008). In logistic regression, there was no effect of baseline severity on binary response (OR=0.995; CI=0.99-1.0; p=0.07). The proportions reaching 50% improvement in pain were 45.4%, 40.9%, 41.3%; in logistic regression, there was a small yet significant impact of baseline severity (OR=1.04; CI=1.03-1.05; p<0.0001). The absolute difference in T-scale scores between responders and non-responders was 0.6 and 0.7 points for binary and 50% improvement, respectively. Neither difference met criteria for clinical relevance. **Conclusions:** The relationships between baseline severity and either the global binary or 50% improvement endpoints are statistically significant, but not clinically relevant. This large meta-analysis provides further evidence that both endpoints are valid as primary endpoints for IBS clinical trials. [Work by Rome Foundation Endpoints Committee]

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Performance of Competing IBS Trial Endpoints Depends On IBS Subtype: Results of the ROME Foundation Endpoints Working Group Meta-Analysis

Brennan M. Spiegel, Roger E. Bolus, Michael Camilleri

Background: It is unclear how best to measure patient reported outcomes (PROs) in IBS trials, and whether IBS subtype should influence the choice of PRO. Binary PROs (*e.g.* adequate relief) may fail to detect minimal clinically important differences (MCID) in symptom improvement. An alternative is to measure improvement on a linear severity scale, and to define response over time of treatment as ≥50% improvement. **Aim:** To perform a meta-analysis of clinical trials to measure the ability of binary endpoints vs 50% improvement criterion to detect MCIDs in symptoms stratified by IBS subtype. **Methods:** We pooled patient-level data from 4 companies comprising 12 IBS trials (N=10,066). Each study included baseline & end-of-study symptom profiles, and an end-of-study binary global endpoint. We created harmonized T-scales for each symptom (mean=100; SD=10) across trials. For the 50% improvement criterion, we adopted abdominal pain intensity as a surrogate for symptom severity, and defined responders as those improving ≥50% over baseline on the pain T-scale. We compared the proportion achieving an MCID for each symptom stratified by responder status for each endpoint (binary vs. 50% improvement), with MCID defined as a net ≥5 point improvement in scale score (i.e. effect size=0.5). **Results:** There were 9044 evaluable subjects (mean age=44; 85% F; 58% IBS-C; 31% IBS-D). The Table displays the results. In IBS-D & IBS-C, both endpoints identified statistically significant differences in the proportion achieving an MCID for pain, bloating, and stool frequency. However, consistency, urgency, and incomplete evacuation were identified in IBS-D, not in IBS-C. The proportion achieving MCID was considerably higher in IBS-D vs IBS-C with both endpoints. **Conclusions:** Global binary & 50% improvement endpoints performed similarly in discriminating between those achieving MCID symptom response vs non-responders, especially for pain, bloat, and urgency. However, there was better discriminant spread in IBS-D vs IBS-C. This suggests that more sensitive endpoints might be necessary for IBS-C. [Work by Rome Endpoint Committee]

Spread in Proportion of Patients with MCID for Bowel Symptoms by IBS Subtype and Response Definition (*=p<0.05).

	IBS-C		IBS-D	
	Binary	50%	Binary	50%
Pain	38%*	56%*	36%*	60%*
Bloat	38%*	52%*	39%*	50%*
Stool Freq	5%*	3%*	28%*	32%*
Stool Consist	10%*	8%	32%*	30%*
Urgency	1%	9%	34%*	41%*
Incomp Evac	6%	13%*	20%*	26%*
Strain	10%	16%*	1%	4%

suicidality except for suicide attempt 5 years later. No ageXpain interactions were significant, but genderXpain was significant for suicide attempt 5 years later (OR=0.27 for girls vs boys, 95%CI 0.1-0.6). In boys abdominal pain and suicide attempt 5 years later were associated (OR=3.1; 95%CI 1.4-7.1) after controlling for depression but not in girls (OR=.97; 95%CI .6-1.7). **Conclusions:** Chronic pain in adolescents is associated with increased suicidality 1 year later independently of depression. In addition adolescent boys who suffer from chronic abdominal pain are at increased risk for suicide attempt in early adulthood. These data suggest the need for increased screening and treatment for suicidality and depression for adolescent pain patients. [Funded by P01-HD31921 NICHD, with cooperative funding from 17 other agencies and R24 DK067674.]

Logistic regression analyses predicting suicidality by chronic abdominal pain

	Suicide Ideation OR (95% CI)		Suicide Attempt OR (95% CI)	
	1 yr later	5 yr later	1 yr later	5 yr later
Chronic abdominal pain	1.9 (1.6-2.2)	1.7 (1.3-2.0)	2.3 (1.8-3.0)	1.9 (1.3-3.0)
Chronic abdominal pain after controlling for depression	1.3 (1.1-1.6)	1.3 (1.0-1.7)	1.4 (1.1-1.9)	1.5 (.9-2.4)

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Symptom Attitudes and Beliefs Predict Severity and Quality of Life in Irritable Bowel Syndrome and Partially Mediate the Effect of Depression On Quality of Life

Elizabeth J. Videlock, Bruce D. Naliboff, Emeran A. Mayer, Lin Chang

INTRODUCTION: Quality of life is impacted by irritable bowel syndrome (IBS) and is influenced by depression. Illness beliefs are important targets of psychological treatments of somatic syndromes. There is evidence that, similar to depression, the effectiveness of cognitive behavioral therapy in irritable bowel syndrome (IBS) is related to strengthening of prefrontal inhibition of limbic circuits, associated with improved cognitions (Goldapple, Arch Gen Psychiatry. 2004; Lackner, Beh Res and Ther, 2006). AIMS: 1) Determine which symptom beliefs are most related to IBS outcomes, 2) Determine if beliefs mediate effects of depression on outcomes, 3) Evaluate the utility of the Survey of Symptom Attitudes(SOSA), a modified version of the well-validated Survey of Pain Attitudes (SOPA, Jenson, 1987) where "gastrointestinal symptoms" replaces the word "pain" in IBS. ETHODS: The SOSA includes 7 scales that assess GI symptom beliefs: control over symptoms, disability, symptoms signify harm, emotion influences symptoms, medication use, others should respond solicitously to symptom behaviors (solicitude), and a medical cure exists for symptoms. Questionnaires measured: global and lower abdominal pain severity (0-20 scales), generic QOL, IBS-related QOL, and depression (HAD). SOSA scales were entered into regression model stepwise following entry of age and sex. RESULTS: Subjects were 182 Rome+ IBS patients (122 F, 60 M). SOSA scores were not affected by sex or bowel habit subtype. Disability was the best predictor of severity and QOL (Table), and it appears to partially mediate the effect of depression on QOL. When disability is included with depression as a predictor of QOL, the variance explained by the model increases (27.4→47.8%), but the contribution of depression decreases (beta:-0.51→-0.27). p<0.05 for all effects and model fits. CONCLUSION: Beliefs that symptoms cause disability were most strongly associated with severity and QOL in IBS, and appear to partially mediate the effect of depression on QOL. These findings may help explain why CBT, gut-directed hypnosis and other psychological treatments designed to alter cognitions about symptoms, are effective in improving QOL in IBS. More importantly, identifying maldaptive cognitions related to IBS severity and QOL may help to increase the efficacy of CBT. Supported by P50 DK64539, and R24 AT002681.

Outcomes	SOSA predictors standardized coefficient (p)	R^2 (x100)	Sample Questionnaire Items
IBS symptom severity	Disability beta = 0.36 (<0.001) Harm beta = 0.22 (0.003) Medical Cure beta = 0.15 (0.037)	25.9	Disability: "If my symptoms continue at their current level, I will be unable to work" Harm: "The symptoms I usually experience are a sign that damage is being done." Medical Cure: "When I find the right doctor, he or she will know how to reduce my symptoms" Emotion: "Stress in my life increases my symptoms"
PCS	Disability beta = 0.62 (0.001)	38.9	
MCS	Emotion beta = -0.38 (<0.001) Disability beta = 0.21 (0.004)	18.9	
QOL IBS	Disability beta = 0.62 (<0.005)	39.6	
Lower GI Pain	Disability beta = 0.30 (<0.005) Harm beta = 0.21 (0.007)	16.6	

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A History of Sexual Abuse and Catastrophizing Have An Impact On IBS Symptom Severity That Is Unrelated to Psychological Distress

Motoyori Kanazawa, Olafur S. Palsson, Miranda A. Van Tilburg, Marsha J. Turner, Syed Ismail M. Thiwan, Lisa M. Gangarosa, Denesh K. Chitkara, Shin Fukudo, Douglas A. Drossman, William E. Whitehead

IBS symptom severity is significantly associated with visceral pain hypersensitivity and comorbid psychological distress (e.g. somatization, anxiety and depression). Patients with IBS are also more likely than control subjects to report a history of sexual abuse and maladaptive coping in the form of catastrophizing. It has been assumed that the impact of sexual abuse on IBS symptom severity is mediated through psychological distress. The aim of this study was to determine whether abuse history and catastrophizing contribute to IBS symptom severity and whether the relationship is mediated by psychological distress. Methods: Subjects were 109 female IBS patients (mean age, 35 years). The IBS Symptom Severity Scale (IBS-SS), which includes questions on the frequency and intensity of abdominal pain, frequency of distention, dissatisfaction with bowel habits, and interference with daily activities, was the dependent measure in a regression analysis. Independent variables were severe sexual abuse (self report of rape), the catastrophizing scale of the Coping Strategies Questionnaire, and the Brief Symptom Inventory-18 (BSI-18) summary score and subscales for somatization, anxiety and depression. Colonic pain threshold was assessed by barostat. Results: Women who reported having been raped (n=30) had significantly higher scores for overall IBS symptom severity ($p<0.05$) and abdominal bloating ($p<0.01$), and they trended to have more intense abdominal pain ($p=0.07$). Abuse history was not correlated with the colonic pain threshold, the catastrophizing scale, or any subscales on the BSI-18. Multiple regression analyses revealed that a significant amount of variance in the overall score on the IBS-SS was explained by these variables ($R^2=0.34$, $p<0.001$); pain threshold ($\beta=-0.34$, $p<0.001$), abuse history ($\beta=0.16$, $p<0.05$), catastrophizing ($\beta=0.28$, $p=0.001$) and the somatization subscale of the BSI-18 ($\beta=0.19$, $p<0.05$). Conclusions: Severe sexual abuse and maladaptive coping contribute significantly and independently to IBS symptom severity. Surprisingly, the contribution of abuse history appears not to be mediated by psychological distress as measured by the BSI-18 or by catastrophizing. The mechanisms linking abuse history to IBS symptom severity are unknown.

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Causal Relationship Between Loss of β-Spectrin (ELF), Its TGF-β Signaling Adaptor Function and a Hereditary Human Gastrointestinal Cancer Syndrome: Beckwith Wiedemann Syndrome (BWS)

Zhixing Yao, Wilma S. Jogunoori, Geeta Upadhyay, Wenguo Yao, Bibhuti Mishra, Lopa Mishra

Hereditary cancer syndromes provide powerful insights into common forms of cancer. They lead to further understanding of the somatic mutations present in sporadic cancers, as well as the function of cell signaling pathways. The β-Spectrin and adaptor protein ELF (Embryonic Liver Fodrin) is a potent regulator of tumorigenesis through its ability to affect TGF-β tumor suppressor function, specifically Smad3 and Smad4 signaling. We show that *elf*$^{+/-}$ and *elf*$^{+/-}$*/Smad3*$^{+/-}$ mice (C57 B6) spontaneously develop multiple cancers and a nearly identical phenotype observed in patients with Beckwith-Wiedemann syndrome (BWS). BWS is a hereditary cancer overgrowth syndrome and epigenetic disorder that remains poorly understood in the majority of cases, and is associated with an 800-fold increased risk of embryonal neoplasms of childhood that include Wilms' tumors, hepatoblastomas, pancreatoblastoma, neuroblastoma, rhabdomyosarcoma, and adrenocortical carcinomas. Results show that: 1) an *elf*$^{+/-}$ and *elf*$^{+/-}$*/Smad3*$^{+/-}$ mice develop the abnormal ear folds, visceromegaly, adrenal cytomegaly and multiple cancers including liver and metastatic pancreatic cancers observed in patients with BWS. 2) Loss of ELF, but not Smad3 or p53 RNA is observed in *elf*$^{+/-}$, *elf*$^{+/-}$*/Smad3*$^{+/-}$ tumors, BWS tissues, BWS cancers and cell lines. 3) Exogenous ELF rescues TGF-β signaling correcting aberrant Smad3 localization, and TGF-β target gene activation in BWS cell lines. 4) ELF-TGF-β signaling is required for suppression of IGF2 signaling, suggesting that the increased expression of IGF2 observed in BWS may be secondary to loss of ELF, and not the causal event in BWS. 5) In 6 of 7 human BWS cell lines and liver, kidney and tongue tissue, MS PCR and bisulphite sequencing consistently demonstrate loss of ELF through DNA methylation of the ELF promoter irrespective of IGF2 LOI status; 6) 5′-aza-2′-deoxycytidine, an inhibitor of DNA methylation, reactivates Elf gene expression in BWS cell lines. Conclusions: Our results suggest that epigenetic regulation of the TGF-β pathway results in the loss of ELF and its crucial Smad3 adaptor function. The loss of the β-Spectrin, non-PH domain's spectrin ELF, is causally related to the genesis and progression of human BWS. In addition, *elf*$^{+/-}$ and *elf*$^{+/-}$*/Smad3*$^{+/-}$ mice provide an important animal model for BWS, as well as to give crucial insight into sporadic lethal cancers such as hepatocellular and metastatic pancreatic cancers observed in the mice and BWS patients.

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Sprouty-2 Is Up-Regulated in Human Colon Cancers and Functions As An Oncogene: Role of C-MET

Cory Holgren, Urszula Dougherty, Francis Edwin, Dario Cerasi, Ieva Taylor, Alessandro Fichera, Marc Bissonnette, Sharad Khare

Background: Studies in *Drosophila melanogaster* showed that Sprouty negatively regulates receptor tyrosine kinase (RTK) signals by inhibiting Ras/ERK pathways. Sprouty is down regulated and appears to function as a tumor suppressor in breast, prostate and liver cancers. The role of Sprouty in colonic neoplasia is unclear, however, since activating K-ras mutations occur frequently in these tumors. Such mutations could potentially block Sprouty inhibition of K-ras signals. We, therefore, examined Sprouty expression in human colon cancers and assessed Sprouty-induced changes in the growth phenotype of K-ras mutant colon cancer cells. **Methods:** Sprouty and c-Met expression in human colon cancers and adjacent colonic mucosa were assessed by Western blotting. HCT116 human colon cancer cells with mutant K-ras were stably transfected with the full-length Sprouty-2 gene under the CMV promoter. Empty vector (EV) and Sprouty transfectants were stimulated with hepatocyte growth factor (HGF) and cell proliferation (WST-1), cell cycle distribution (FACS) and cell migration (Boyden chamber) were assessed. Xenografts of Sprouty transfectants or EV cells were established in nu/nu mice. Surgical orthotopic tumor implantation was used to assess the potential of transfectants to metastasize to liver and lungs that were detected by H&E staining. We assessed cell proliferation (Ki67), apoptosis (cleaved caspase-3) and angiogenesis (nestin-1) in tumor xenografts by immunostaining. **Results:** Sprouty-2 was significantly upregulated in > 80% human colonic adenocarcinomas compared to adjacent mucosa ($p<0.05$). Strikingly, the c-Met receptor was also up-regulated in tumors with increased Sprouty-2. Three poorly differentiated adenocarcinomas with lymphatic or vascular invasion demonstrated >10 fold increases in c-Met and Sprouty. Compared to EV, Sprouty transfectants demonstrated strong up-regulation of c-Met that was functional as HGF stimulated cell proliferation (130% of EV $p<0.05$), accelerated G1 to S cell cycle transition and enhanced

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Functional Brain-Gut Research Group

FBG

The mission of the Functional Brain-Gut Research Group is to support, promote and advance multidisciplinary research and education in the basic science, clinical and behavioral aspects of brain-gut interactions.

Emeran Mayer, MD
President

Message from the President

Taking over the presidency of an organization with a long tradition always comes with an obligation to help fulfill the dreams and aspiration of the founders and previous leaders. With this obligation in mind, I am fully aware and appreciative of Doug Drossman's vision and efforts, which together with the help of the early giants in the field (Marvin Schuster, Bill Whitehead, Nick Talley, Grant Thompson and Joel Richter) launched an organization in 1989 "*to support, promote and advance multi-disciplinary research and education in the basic science, clinical and behavioral aspects of brain gut interactions.*" Most people in the field today, do not remember that IBS and other functional GI disorders (FGIDs) were either not accepted as "real" disorders at the time, or were explained as simple manifestations of GI smooth muscle dysfunction. Over the next 20 years, under different leaders, the organization has lived up to its mission with remarkable success, regardless if measured in terms of membership, publications, visibility or legitimization of the field of FGIDs. Probably the most visible expression of this success is the fact that the FBG is now a major player (together with ANMS, ENMS and the INMG) in the publication of the highly successful Neurogastroenterology and motility (NGM) journal, and in the organization of the Annual Joint International Meetings in Neurogastroenterology. As all of you hopefully know, the FBG was part of the planning committee for the upcoming Joint International Neurogastroenterology and Motility meeting in Lucerne, Switzerland, Nov. 6-9, 2008 (www.ngm2008.com), and is the host for next year's Joint International Meeting in Chicago (Aug. 26-30, 2009). Under the leadership of the FBG, an exciting agenda has been developed for the Chicago meeting and the fundraising process is under way. Also, starting with Lin Chang's vision and early leadership, the FBG's Young

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June 2, 2009

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Cross Cultural Perspective of Irritable Bowel Syndrome in Japan

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This column has been submitted by Dr. Shin Fukudo and is based on his extensive experience in research and treatment of patients with Irritable Bowel Syndrome in Sendai, Japan. A number of topics and questions were submitted to Dr. Fukudo, mainly focused on cultural and psychological influences on the illness experience of IBS patients. His response reflects some of the particular differences between Japan and other geographic locations, consistent with columns previously published in the FBG newsletter.

Introduction
Irritable bowel syndrome (IBS) is one of the most common diagnoses in gastroenterological practice in Japan. A recent nation-wide survey revealed that Rome II-defined IBS was diagnosed in 196 patients (31%) from 633 patients who visited a medical out-patient clinic in Japan (1). The prevalence of Rome-II defined IBS in subjects seen for annual health screening examinations in the general population was 14.2% (2). Despite differences in race, culture, and medical system, general epidemiological data of IBS in Japan are very similar to the Western countries. However, there are some unresolved issues.

Culture, beliefs and irritable bowel syndrome
Japan is an isolated country on the east coast of the pan-pacific rim. Japanese people belong to the mongoloid race but their language is unique. Isolated geography and an original religion (Shintoism) made Japanese culture independent from other countries in Asia. Japanese culture has been more recently influenced by foreign countries and it has synthesized the new cultures with unique aspects. A typical example is Bushido, the Samurai way of life. For more details, read the book by Inazo Nitobe. Otherwise, see movies by Akira Kurosawa.

Japanese culture has a unique belief in the relation between mind (shin or kokoro) and body (shin or karada). They are not mutually exclusive. In Japan, there is a famous phrase "shin-shin-ichi-nyo". The first shin is mind and the second shin is body. "ichi-nyo" means all together and not mutually exclusive. Most Japanese easily understand this. There are many Japanese ways to express one's mind with words from the gastrointestinal (GI) tract. For example, "moving gut" means getting angry and "showing inside the belly" means talking without concealing one's secret.

The biopsychosocial concept of IBS
The Western style of medicine was imported to Japan in the 19th century. Over-adaptation to the biomedical approach led to the specialization of medicine. The traditional Japanese view of mind-body relationship was not so respected until the 1950s. Most internists and gastroenterologists tended to diagnose in a dichotomized way; either purely organic disease or purely psychogenic disease. In contrast, development of the Japanese Society of Psychosomatic Medicine since 1958 has gradually reversed this simplistic concept of organic-psychogenic dichotomy.

There are still many patients, family members, and non-specialist physicians who believe that IBS is entirely organic or entirely psychogenic. Patients who have a concept of IBS as entirely organic usually receive multiple tests in different medical institutions. Because the discovery and eradication of Helicobacter pylori minimized the role of psychosocial stress in peptic ulcer disease, some physicians predict a similar fate in IBS. Physicians who have a concept of IBS as entirely psychogenic usually refer IBS patients to psychiatrists but IBS patients usually refuse to consult with psychiatrists.

To strengthen the clinical practice, research, and education of biopsychosocial aspects of medical illness, the Japanese Society of Psychosomatic Medicine developed the open-access English e-journal named Biopsychosocial Medicine (http://www.bpsmedicine.com/), in which Shin Fukudo (Deputy Editor) and Douglas A. Drossman (Advisory Board) play roles.

Psychological experience
Traditionally, symptoms of functional dyspepsia are called "weak stomach" and those of IBS are called "weak gut". In Japanese culture, individuals who can eat many foods or who have no concern about bathroom locations are considered to be healthy. Neurotic or depressive individuals often complain of anorexia, weight loss, constipation, diarrhea, or bodily pain. There are several novels describing such people. Most Japanese have an image of individuals with sustained GI symptoms, as neuroticism. It is rare that individuals with functional GI disorders are recognized to have significant illness.
Recently, individuals with IBS symptoms are recognized as those who have knowledge of the location of bathrooms in subway or railroad stations inside the large cities. Individuals with IBS do not have enough time to defecate at home in the morning. They must take trains or subways for more than an hour to go to work or to school. Usually there is heavy crowd traffic in the morning at Tokyo, Osaka, or the other large cities in Japan. Therefore, individuals with IBS are stressed every morning and feel abdominal pain/discomfort with urgency for defecation. In the worst case, they have to get off the train on the way to work or school and use the bathroom inside the station.

Children in the elementary school in Japan are also placed in a difficult situation. For children, defecation in school is behavior to be stigmatized. This is an irrational belief but is often overlooked by teachers. Gas symptoms (flatus and abdominal bloating) are also stigmatized. Social anxiety disorder (social phobia) is often overlapped with some categories of functional bowel disorders. Entrance examinations to university, high school, or even junior high school consist of typical psychosocial stressors in adolescence.

The role of psychosocial stress (1) and negative emotions, especially depression and anxiety (2) in IBS, have been published.

Gender issue of IBS
There is evidence for sex- and gender-related differences in IBS prevalence in the Western countries (3). In contrast, Japanese data from medical out-patient clinic depicted that there was no definitive difference in prevalence of IBS between men (27.5%) and women (34.1%)(1). There was no definitive difference in prevalence of IBS between men (12.9%) and women (15.5%) in epidemiologic data either (2). However, an impact of female sex on constipation

was found (2). Therefore, determining factors which minimize the gender effect of IBS in East Asian countries may be useful for developing prevention or new therapy for female IBS patients in western countries.

Health care utilization

Probably the Japanese medical system is one of the most cost-effective systems in the world. All people in Japan have medical insurance and patients can freely access their favorite clinics or hospitals.

Despite relatively reasonable cost, many individuals with IBS symptoms do not consult physicians. There is not enough being done to generalize the concept that functional GI disorders are significant illnesses. Many IBS individuals take OTC drugs with scopolia extract (an anticholinergic) before taking subways or going to school. Recently, IBS patients in Japan who visit clinics or hospitals are often treated with a guideline (3). The guideline is made from systematic steps including pharmacotherapy and psychotherapy. A new 5-HT3 antagonist ramosetron has been approved by the Ministry of Health, Welfare, and Labor of Japan for male patients with IBS-D.

There are some specific treatments for IBS in Japan. One is the Chinese herbal medicine (Kampo). Kampo was originated from China but greatly modified and developed in Japan. For IBS, Keishi-ka-shakuyaku-to or Dai-ken-chu-to is frequently prescribed. Another treatment is fasting therapy (4,5). Fasting therapy is an original treatment for IBS in Japan. It consists of complete fasting for 10 days and recovery for 5 days with intensive psychotherapy.

Editorial comment by Charles and Mary-Joan Gerson

Japan appears to suffer from some of the difficulties experienced by the IBS population in other countries. Patients are seen as neurotic and probably identify themselves as neurotic. What is different in Japan is a history of a strong mind-body concept, clearly not mutually exclusive, that has been displaced by modern medical thinking. However, the use of GI terminology to express emotional feelings and the common understanding of "shin-shin-ichi-nyo" represents a sustained cultural belief and is probably one reason that IBS patients don't consult physicians and use complementary remedies.

The issue of shame attached to GI symptoms, need to find a bathroom on the way to work, need to be excused from class to use the toilet, represents an aspect of Japanese culture. This is probably aggravated by the pace of life, rushing to work in crowded conditions, experiencing competitive stresses at school. In addition, functional GI symptoms are seen as representing weakness and neuroticism. Thse factors can have a profound psychological effect on a patient with IBS. The participation of psychology professionals in the care of these patients is important and is part of Dr. Fukudo's guideline for treatment of IBS. However, resistance of Japanese to psychological referral is a confounding factor.

All of these issues are challenging. The organizations in Japan described by Dr. Fukudo that are designed to focus on functional GI disorders will hopefully lead the way to better care for the Japanese IBS population.

Drs. Charles and Mary-Joan Gerson

Future direction

In order to find true impact of different cultures on IBS, international criteria (Rome III) and validated questionnaires (6, 7) are indispensable. Full Japanese translation of the Rome III book will soon be published. Gene-environmental interactions on IBS features should be tested in different populations because some genetic polymorphisms have racial differences (8).

There are active societies on IBS research in Japan; Japanese Society of Gastroenterology, Japanese Society of Psychosomatic Medicine, and Japanese Society of Neurogastroenterology and Motility. Asian countries have created the Asian Neurogastroenterology and Motility Association (ANMAI. I believe that mutual and reciprocal interactions between FBG/Rome Committee and these societies will produce fruitful results.

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脳腸相関による消化管機能制御

Regulation of Gastrointestinal Function by Brain-Gut Interactions

福土 審
Shin Fukudo

生物心理社会モデルによる心身医学的なアプローチがその威力を発揮する代表的な疾患群として機能性消化管障害(functional gastrointestinal disorders)が挙げられる．過敏性腸症候群(irritable bowel syndrome；IBS)はその概念形成の源流となった疾患である．機能性消化管障害，特にIBSの研究と臨床は，既知の生物学的診断マーカーが未発見である疾患の国際的診断基準作成，脳-末梢臓器相関の概念化，脳機能画像の導入，ストレス病態からの関連物質の絞り込み，炎症と感作の関連，遺伝子と環境の関連，性差医学，薬物療法と心理療法の組み合わせなどの多くの点で他疾患に応用できる先進性を含んでいる．

key words　IBS，脳腸相関，消化管運動，内臓(消化管)知覚，PET，粘膜炎症

はじめに

現代は多くの疾患の心理面が重視される社会情勢にある．George Engelの生物心理社会モデル(biopsychosocial model)は，疾病の理解に生物学的要因だけでなく，心理社会的要因の関与も分析し，総合的に疾病を把握する試みである[1]．機能性消化管障害(functional gastrointestinal disorders)は，生物心理社会モデルがその威力を発揮する代表的な疾患群である[2]．その概念形成の源流となったのが過敏性腸症候群(irritable bowel syndrome；IBS)である[2]．機能性消化管障害，特にIBSの研究と臨床は，多くの点で先進性を含んでおり，その進歩に我が国の科学も貢献している．

後述するように，IBSは内臓機能と脳機能が関連する脳腸相関の病態を持つ．文部科学省科学技術政策研究所から，基礎研究を中心とする科学の動向(2001～2006年)を俯瞰的に示す「サイエンスマップ2006」が公表されている[3]．科学全体の中でも，“内臓感覚と情動・共感の神経機構”の研究が，最近急速に出現してきたテーマであり，勃興しつつある注目研究領域の1つであることがわかる(図1)．

Ⅰ 機能性消化管障害のRome Ⅲ診断基準

機能性消化管障害とは，消化器症状が慢性・再発性に持続する一方で，その症状が通常の臨床検査で検出される器質的疾患によるものではない障害である[4]．その代表的な障害がIBSである．IBSの中核の症状は腹痛とそれに関連

■図1　科学研究の動向に占める“内臓感覚と情動・共感の神経機構”の研究の位置

■表1 機能性消化管障害[2)]

(A)機能性食道障害
A1:機能性胸焼
A2:機能性食道性胸痛
A3:機能性嚥下困難
A4:食道球

(B)機能性胃十二指腸障害
B1:機能性ディスペプシア
B1a:食後不快症候群(PDS)
B1b:上腹部痛症候群(EPS)
B2:曖気障害
B2a:空気嚥下症
B2b:非特異過剰曖気障害
B3:悪心嘔吐障害
B3a:慢性特発性悪心
B3b:機能性嘔吐
B3c:周期性嘔吐症候群
B4:成人反芻症候群

(C)機能性腸障害
C1:過敏性腸症候群(IBS)
C2:機能性膨満
C3:機能性便秘
C4:機能性下痢
C5:非特異機能性腸障害

(D)機能性腹痛症候群(FAPS)

(E)機能性胆嚢・Oddi括約筋障害
E1:機能性胆嚢障害
E2:機能性胆道Oddi括約筋障害
E2:機能性膵臓Oddi括約筋障害

(F)機能性直腸肛門障害
F1:機能性便失禁
F2:機能性直腸肛門痛
F2a:慢性直腸肛門痛
F2a1:肛門挙筋症候群
F2a1:非特異機能性直腸肛門痛
F2b:消散性直腸肛門痛
F3:機能性排便障害
F3a:失調性排便
F3b:不適切排便推進症

(G)新生児・幼児機能性消化管障害
G1:乳児逆流症
G2:乳児反芻症候群
G3:周期性嘔吐症候群
G4:乳児腹痛
G5:機能性下痢
G6:乳児排便困難
G7:機能性便秘

(H)小児・思春期消化管機能障害
H1:嘔吐・空気嚥下症
H1a:思春期反芻症候群
H1b:周期性嘔吐症候群
H1c:空気嚥下症
H2:腹痛関連機能性消化管障害
H2a:機能性ディスペプシア
H2b:過敏性腸症候群
H2c:腹部片頭痛
H2d:機能性腹痛
H2d1:小児機能性腹痛症候群
H3:便秘・便失禁
H3a:機能性便秘
H3b:非貯留性便失禁

■表2 IBSのRome Ⅲ診断基準[7)]

■腹痛あるいは腹部不快感が
■最近3カ月の中の1カ月につき少なくとも3日以上を占め
■下記の2項目以上の特徴を示す
①排便によって改善する
②排便頻度の変化で始まる
③便形状(外観)の変化で始まる
* 少なくとも診断の6カ月以上前に症状が出現し,最近3カ月間は基準を満たす必要がある.
** 腹部不快感とは,腹痛とは言えない不愉快な感覚を指す.病態生理研究や臨床研究では,腹痛あるいは腹部不快感が1週間につき少なくとも2日以上を占める者が対象として望ましい.

した便通異常であるが,大腸内視鏡検査では異常は見られない.これらの疾患群は特定の検査値によって診断できるものではないために,国,また立場や見解の相違によって診断が異なるという事態を生み,それがまた,特異的な病態生理の同定を阻むという事態を招いていた.

この事態が動いたのが1988年のRomeにおける国際消化器病学会である[2)].このときに,IBSの国際的な診断ガイドラインが提唱され,翌年に公表された.IBSが明確に定義されると,IBSに類似しているがIBSとは言えない多くの障害を同時に定義する必要が生じる.腹痛・腹部不快感のない下痢は,IBSではなく機能性下痢と定義する.また,腹痛・腹部不快感のない便秘もIBSではなく機能性便秘である.これらの疾患群が機能性腸障害であり,機能性腸障害がこのように明確に同定されると,機能性腸障害に類似しているが,症状を作り出す消化管の部位が異なる他の障害も同時に定義しなくてはならない.便通異常のない腹痛は機能性腸障害ではなく,このような患者は機能性腹痛症候群と診断すべきである.以上のような議論が様々な国の医師で構成されるワーキングチームで交わされ,最初の国際的な診断基準であるRome基準が1990年に発表され,成書として1994年に公刊された[4)].これを契機として,機能性消化管障害の診断基準統一の気運が高まり,改訂版であるRome Ⅱ基準が1999年に公表された.Rome Ⅱ基準は国際的に普及し,機能性消化管障害の診断,治療,研究,創薬などあらゆる面を活性化した[2)].

その改訂版が2006年に公刊された.これがRome Ⅲ基準である[2),4)].その過程には日本人研究者も貢献している[5),6)].機能性消化管障害は成人の食道,胃・十二指腸,小腸・大腸,胆道・膵管,直腸・肛門のそれぞれの部位の障害と機能性腹痛症候群の6障害(A～F),ならびに新生児・幼児と小児・思春期の2障害(G, H)の合計8障害からなる(表1)[2),4)].そのすべての障害の診断基準が国際的に統一されている.以上から,国,また立場や見解の相違によって診断が異なるという事態はすでに過去のものとなったと言えよう.

Ⅱ IBSのRome Ⅲ診断基準

Rome Ⅲ基準においては,IBSは表2のように定義されている[7)].また,IBSはBristol便形状尺度(表3)の頻度に基づいて4型に分類されている(表4)[2),7)].その根拠は,排

■表3 Bristol便形状尺度[7]

型	説明
1	分離した硬い木の実のような便(排便困難を伴う)
2	硬便が集合したソーセージ状の便
3	表面にひび割れがあるソーセージ状の便
4	平滑で柔らかいソーセージ状あるいは蛇状の便
5	柔らかく割面が鋭い小塊状の便(排便が容易)
6	ふわふわした不定形の小片便,泥状便
7	固形物を含まない水様便

■表4 IBSの分類(Rome Ⅲ)[7]

❶便秘型IBS(IBS-C)
硬便 or 兎糞状便[a]が便形状が25%以上,かつ,
軟便 or 水様便[b]が便形状の25%未満[c]
❷下痢型IBS(IBS-D)
軟便 or 水様便[b]が便形状の25%以上,かつ,
硬便 or 兎糞状便[a]が便形状の25%未満[c]
❸混合型IBS(IBS-M)
硬便 or 兎糞状便[a]が便形状の25%以上,かつ,
軟便 or 水様便[b]が便形状の25%以上[c]
❹分類不能型IBS(IBS-U)
便形状の異常が不十分であって,
IBS-C, IBS-D, IBS-Mのいずれでもない[c]

a;Bristol便形状尺度1型2型
b;Bristol便形状尺度6型7型
c;止瀉薬・下剤を用いないときの糞便で評価する

便頻度よりも便形状が下部消化管機能をより反映するためである.これらの型は相互移行の頻度が70～100%に及ぶ.IBSは機能性消化管障害の原型であり,その病態も機能性消化管障害の中で最も良く分析されている.IBSは有病率が10～20%と高頻度であり,患者のQOL(quality of life)が低く,患者個人と医療全体双方の経済に悪影響を及ぼすことから重要な疾患である[2].

Ⅲ 脳腸相関

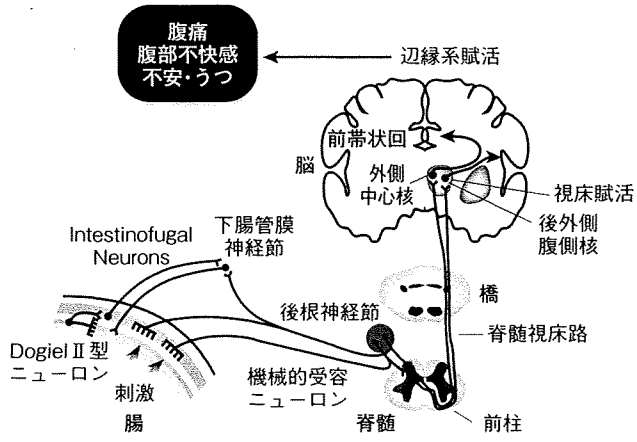
脳腸相関(brain-gut interactions)という概念[8]により,IBSの病態生理が理解されている(図2).日常臨床では"心理社会的ストレスによってIBS患者の消化器症状が発症もしくは増悪する"という現象がその典型例である[8].これは脳から腸に向かう関係である.逆に,腸から脳に向かう関係もIBSでは重要である[2].これは日常臨床では"消化管刺激に対する内臓知覚が過敏である"という現象として現れる.種々の脳機能画像により,脳腸相関が科学的かつ視覚的に分析できる.PET(positron emission tomography)あるいは機能的核磁気共鳴法(functional MRI)を用いた検討により,大腸伸展刺激時のヒト消化管知覚の脳内プロセシングと神経伝達が明らかになりつつある(図3)[9].これらの脳機能画像を用いて大腸伸展刺激時の局所脳血流量の変化を見ると,健常者で見られる前帯状回の賦活が,IBS患者ではさらに亢進しており,ときに前頭前野の賦活化が見られる[2].これらより,IBSの消化管知覚の脳内プロセシング異常が示唆される.

PETで得られたIBSの消化管知覚における脳内プロセシング異常は,大脳誘発電位によっても明らかになりつつある.大腸の拡張刺激に対する大脳誘発電位を導出すると,IBSにおいてはN_1, P_1, N_2の3相波の潜時が短く,振幅が大きく,同様の現象が機能性ディスペプシア[注1]においても見られる[10].IBS患者に見られる内臓知覚過敏の重要な原因として,消化管から中枢に伝達される信号の処理過程が感作されている病理が示唆される.

Ⅳ IBSにおけるCRHの役割

IBSの脳腸の病態生理を一元的に説明しうる有力な物質が脳と腸の双方に豊富に存在するCRH(corticotropin-releasing hormone)(図4)である[11].IBSの心理的異常としては抑うつと不安が多い[2].CRHはこれらの心理的異常と関

注1 辛いと感じる食後のもたれ感,早期飽満感,心窩部痛,心窩部灼熱感のいずれか1つ以上があり,症状の原因となる器質的疾患が上部消化管内視鏡検査を含む検査で除外されているもの.症状は6カ月以上前から生じ,最近3カ月は上記基準を満たしているもの.



■図2 脳腸相関:消化管から脳に向かう経路の模式図