Autonomic nervous system activity in constipation-predominant irritable bowel syndrome patients

Marcel Mazur\(^1\), Agata Furgała\(^1\), Konrad Jabłoński\(^2,3\), Tomasz Mach\(^2,3\), Piotr Thor\(^1\)

\(^1\) Department of Pathophysiology, Jagiellonian University, Medical College, Cracow, Poland
\(^2\) Department of Gastroenterology and Hepatology, Jagiellonian University Medical College, Cracow, Poland
\(^3\) Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital, Cracow, Poland

Source of support: The study was supported by a grant from the State Committee For Scientific Research, Warsaw, Poland (KBN 2 P05B 044 27)

Summary

Background: The main mechanism underlying irritable bowel syndrome is currently believed to be a dysfunction of the brain-gut axis. Autonomic nervous system dysfunction can contribute to development of irritable bowel syndrome symptoms by disturbing visceral sensations.

Material/Methods: Thirty patients with a diagnosis of constipation-predominant irritable bowel syndrome and 30 healthy volunteers were included in the study. Resting and functional autonomic nervous system tests and percutaneous electrogastrography were performed. Plasma adrenalin, noradrenalin, insulin, ghrelin and cholecystokinin activity was analyzed.

Results: Increased sympathetic activation with disturbed parasympathetic function was demonstrated. Patients had substantially higher plasma catecholamine concentration, which confirms sympathetic overbalance. Hyperinsulinemia may explain sympathetic predominance followed by gastric and intestinal motility deceleration. Abnormal, reduced ghrelin and cholecystokinin titre may disturb brain-gut axis functioning and may be responsible for gastric motility deceleration. In electrogastrography, distinctly lower values of fasting normogastria percentage and dominant power were observed. Patients had substantially lower slow wave coupling percentage both in fasting and post-prandial periods, which negatively correlated with plasma catecholamines level. Gastric myoelectrical activity disturbances may result from lack of sympatho-parasympathetic equilibrium.

Conclusions: Central sympathetic influence within the brain-gut axis is most probably responsible for myoelectrical activity disturbances in irritable bowel syndrome patients.

key words: irritable bowel syndrome • autonomic nervous system activity • heart rate variability • gastric myoelectric activity • electrogastrography

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/883269

Word count: 3173

Tables: 9

Figures: –

References: 50

Author’s address: Marcel Mazur, Department of Pathophysiology, Jagiellonian University Medical College, Kopernika 19E-1 St., 31-501 Cracow, Poland
BACKGROUND

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder in which bowel function is altered (diarrhoea or constipation) in association with abdominal pain or discomfort. The worldwide prevalence among adults exceeds 10% [1]. Symptoms occur in up to 50% of patients referred to gastroenterology clinics [2,3]. The age at onset varies, with the peak in the third and fourth decades of life. The disorder has a female predominance (2:1 ratio). According to the commonly accepted definition, no mechanical, biochemical, or overt inflammatory condition explains the presence of symptoms [1]. Therefore, the diagnosis of the irritable bowel syndrome is based solely on individual complaints in the absence of “alarm” symptoms (pain or diarrhoea that awakens/interferes with sleep, visible or occult blood in stool, weight loss, fever, abnormal physical examination) and exclusion of obvious organic diseases and structural alterations [4–6].

The pathogenesis of the irritable bowel syndrome remains unsolved since mechanisms leading to alteration of the gut function related to particular symptoms are unclear. The main gastrointestinal sensory-motor dysfunction in irritable bowel syndrome is consistent with an up-regulation in neural processing between the gut and the brain (brain-gut axis) and results in alterations in gut motility, secretion, and visceral sensation. There is also an increasing acceptance that the central nervous system, an important component of the brain-gut axis, plays an important role in development of symptoms in the response to stress as an effect underlying affective disorder [7]. The autonomic nervous system mediates brain-gut interactions. Serotonin, a key mediator of gut motility, secretion, and sensation, has been found to mediate this bi-directional brain-gut communication [8], but studies have shown that cholecystokinin and ghrelin are also involved in gut-brain signalling [9,10]. Since 1928, when Bockus suggested that imbalance of the autonomic nervous system was responsible for IBS, attention has been focused on the dysfunction of the autonomic nervous system (ANS) [11–16]. The aim of this study was to evaluate changes in ANS activity and its correlation with gastric myoelectric activity in constipation-predominant IBS patients.

MATERIAL AND METHODS

Thirty patients (18 women, 12 men; 42.2±14 yrs) with constipation-predominant IBS (IBS-C) and 30 healthy volunteers (19 women, 11 men, 38.9±11.6 yrs) were included in the study (Table 1). To diagnose patients with the constipation-predominant form of IBS, Rome III criteria were used [4]. We excluded patients with diabetes mellitus, obesity (defined according to WHO as BMI >30 kg/m²), alcoholism, cardiovascular (hypertension, coronary artery disease, valvular heart disease, cardiac arrhythmias) and neurological diseases, medications possibly interfering with heart rate variability measurement, gastrointestinal pathology (e.g., inflammatory bowel disease) or surgery, renal, or gynaecological pathology that might have resulted in IBS symptoms (e.g., bowel resection, endometriosis). We also excluded patients taking specific medications for IBS on a regular basis (e.g., antidiarrheals, laxatives, antispasmodic agents, tricyclic antidepressants, serotonin-3-receptor antagonists or serotonin-4-receptor agonists, 3 or more times a week).

All participants involved in the study were informed about examinations to be carried out and they all gave their consent in writing to all examinations. The study was approved by the Jagiellonian University Bioethics Commission.

All studies were performed in the Department of Pathophysiology of Jagiellonian University Medical College. After overnight fasting, autonomic activity assessed by HRV with a Task Force Monitor 3041 (CNSystems, Austria) and gastric myoelectric activity recorded using a 4-channel electrogastrography (EGG) recorder (Medtronic, USA) in basal conditions and after a standard meal 30 minutes each (Nutridrink 300 kcal, Nutricia, Poland) were measured simultaneously in both groups. In the HRV recording, the frequency domain analysis parameters: LF – power of spectra of low 0.04–0.15Hz frequency; HF – power of spectra of high 0.15–0.4Hz frequency; based on the fast Fourier transformation (FFT) were calculated. In the electrogastrography analysis the following parameters were evaluated: dominant frequency (DF); dominant power of dominant frequency (DP); percentage of normo-, brady- and tachygastria (0.5–2 cpm – bradygastria; 2–4 cpm – normogastria; 4.0–9.0 cpm – tachygastria), percentage of dysrhythmia and arrhythmia time; and percentage of slow-wave coupling between channels 3–4 (%SWC).

HRV recording in resting conditions was followed by the deep breathing test (DBT), which lasted 5 minutes. Apart from registering HRV, E/E (ratio of the longest and the shortest RR period during the test), DBD (deep breathing difference, the difference between the maximum and minimal heart rate during the test) and RSA amplitude (respiratory sinus arrhythmia, the difference in the heart rate at the end of exhalation and at the end of the inhalation) values were determined.

The tilt test was conducted by picking a patient up passively on a bed equipped with a electro-hydraulic servomotor with a 60° slope, in which position the patient stayed in through 5 minutes, and afterwards he returned to the horizontal position [17]. A bisectional electro-hydraulic tilt table (Manumed, Enraf Nonius, Netherlands) was used.

During the Valsalva manoeuvre, the patient being examined, after the previous rest, exhaled air into the mouth-piece of the manometer for 15 seconds, causing the pylon of mercury to reach the value of 40 mmHg. During the entire attempt, a permanent registration of the electrocardiography and the arterial pressure was conducted.

The hand grip test performed for 5 minutes, in which an examined person was gripping the dynamometer with a power of 30% of maximum strength of the contraction of the hand achieved before the attempt. Blood pressure was measured continuously during the test. In the examination we determine the difference between the value of the diastolic blood pressure after finishing the contraction, and value before beginning the test [18], using a manual hydraulic dynamometer (Jamar, Preston, USA).

Fasting plasma hormone levels were measured in both groups. Blood samples were stored at 2–8°C until centrifuged to separate the plasma within 2 hours after blood collection (at 3800g at 8°C for 10 minutes). The supernatant was aspirated and stored from 6 h to 1 month at −20°C until analysis. Analyses of plasma adrenaline and noradrenaline concentrations were
performed with Adrenaline and Noradrenaline ELISA kit (CatCombi ELISA, IBL, Germany, test sensitivity 20 pg/ml) for automated systems. Analysis of plasma ghrelin concentration was performed with Human Unacylated Ghrelin ELISA (BioVendor, USA, test sensitivity 0.2 pg/ml) for automated systems. Analysis of plasma insulin concentration was performed with the INS-EASIA kit (BioSource Europe S.A., Belgium, test sensitivity 0.17 µIU/ml) for automated systems. Analysis of cholecystokinin (CCK) was performed with the ELISA kit (Bender MedSystems, Austria, test sensitivity 1.65 ng/ml) for automated systems. All analyses were performed according to suppliers’ instructions. Absorption readout was done using a PowerWave ELx800 reader (BioTek, USA) with a 450 nm wavelength. Substance concentration value was read off from the curve delineated for hormone concentration standards expressed in appropriate units. Assays were done in duplicates.

Numerical data are given as the arithmetic means and standard deviations (x ±SD). Statistical analysis was carried out with the help of the statistical package STATISTICA 8.0 for Windows (StatSoft Inc., Tulsa, Oklahoma, USA). In calculations, a parametric test was applied for comparing value of average findings for patients and persons from the control group. We used model IV, which is a test in which statistics (test function) ‘Z’ have normal distribution, and critical values were read off from boards. In case of lack of normal distribution, the III model of the same test, with Cochran-Cox ‘C’ statistics, was used, for which critical values were enumerated, not read out from boards. The hypotheses in this case had the form: null hypothesis H0: m 1=m 2, against the alternative hypothesis H1: m 1 ≠ m 2. Statistical significance was set at p<0.05. Assessment of interdependence was made with the help of Pearson correlation. The correlation between HRV parameters, EGG parameters and plasma catecholamine was evaluated by analyzing the relationship between HRV power spectral parameters (LF, ln LF, HF, ln HF) and plasma catecholamine levels (adrenaline, noradrenaline), as well as EGG parameters (percent of dysrhythmias, DF, DP, SWC) and plasma catecholamine levels.

**RESULTS**

Resting HRV parameters were lower in IBS patients in comparison with the control group: LF – 833.2±849.6 vs. 1176.7±790.6 ms²; HF – 716.1±769.1 vs. 1535.3±1359.5 ms²; yet LF/HF-RRI ratio was higher in patient group: 2.2±1.8 vs. 1.3±1.1; p<0.05, respectively (Table 2).

In DB test HF value was lower than in resting conditions with autonomic balance shifted towards LF value. LF/HF-RRI increased in both groups (Table 3).
Analyses of ANS activity indices revealed abnormal value of 30/15 ratio in the patient group (p<0.05) indicating parasympathetic dysfunction (Table 4). The remaining indices values were in the normal range. Such a result may indicate recent ANS damage.

The fasting plasma level of adrenaline and noradrenaline in IBS patients was higher – 7.67±8.19 vs. 0.38±0.19 nmol/L, and 38.76±29.63 vs. 1.68±0.63 nmol/L, p<0.05, respectively (Table 5).

In IBS-C patients lower ghrelin (187.39±104.02 vs. 257.49±88.04 pg/ml) and cholecystokinin (0.23±0.13 vs. 3.28±1.79 ng/ml) plasma concentrations were observed. Insulin concentration was substantially higher in patients (14.87±13.7 vs. 7.87±2.6 µIU/ml), p<0.05, respectively (Table 6).

Fasting IBS patients showed higher gastric arrhythmia recording time (28.82±13.45% vs. 8.5±8.47%), and dominant power (DP) was lower (60675.68±109922.77 vs. 108857.5±130405.6 µV²) (Table 7). Feeding improved arrhythmia to 20.05±11.03% vs. 5.21±5.93% and DP 93225.19±184659.15 vs. 147460.6±144437.2 µV² in both groups (Table 8). Average slow wave coupling percentage was also lower – 55.99±9.46% in IBS patients vs. 77.44±11.89% in the control group in the fasting period and 62.46±12.63 vs. 82.65±10.78%, respectively, in the postprandial period (Table 9) (p<0.05 in all cases).

There were no statistically strong correlations between resting HRV parameters and EGG. We did not observe statistically significant correlation between HRV parameters and ANS activity.

### Table 4. Autonomic nervous system activity indices.

| ANS test             | Parameter | Patients       | Controls       |
|----------------------|-----------|----------------|----------------|
| Deep breathing test  | E/I       | 1.25±0.13      | 1.27±0.05      |
|                      | DBD       | 207.33±96.04   | 230.8±52.29    |
| Valsalva manoeuvre   | VR        | 1.47±0.29      | 1.41±0.21      |
| Tilt test            | 30/15     | 1±0.09         | 1.23±0.14      |
| Hand grip test       | Δ diastolic BP | 23.03±16.2 | 20.33±6.42     |

E/I – inspiratory to expiratory ratio of the longest and the shortest RR interval; DBD – deep breathing difference; VR – valsalva ratio; BP – blood pressure.

### Table 5. Plasma catecholamines concentrations.

| Catecholamines         | Patients       | Controls       |
|------------------------|----------------|----------------|
| Adrenaline [nmol/l]    | 7.67±8.19      | 0.38±0.19      |
| Noradrenaline [nmol/l] | 38.76±29.63    | 1.68±0.63      |

### Table 6. Plasma gut hormones concentrations.

| Gut hormones        | Patients       | Controls       |
|---------------------|----------------|----------------|
| Ghrelin [pg/ml]     | 187.39±104.02  | 257.49±88.04   |
| Cholecystokinin [ng/ml] | 0.23±0.13    | 3.28±1.79      |
| Insulin [IU/ml]     | 14.87±13.7    | 7.87±2.6       |

### Table 7. Fasted electrogastrography parameters.

| Fasted electrogastrography parameters | Patients       | Controls       |
|--------------------------------------|----------------|----------------|
| DF (cpm)                             | 3.02±0.66      | 3.0±0.27       |
| DP (µV × µV)                         | 60675.68±109922.77 | 108857.5±130405.6 |
| Normogastria (%)                     | 55.35±18.95    | 85.95±12.26    |
| Bradygastria (%)                     | 9.14±7.01      | 2.62±4.28      |
| Tachygastria (%)                     | 6.79±7.02      | 2.64±3.7       |
| Arrhythmia (%)                       | 28.82±13.45    | 8.5±8.47       |

DF – dominant frequency; DP – dominant power of dominant frequency.

### Table 8. Fed electrogastrography parameters.

| Fed electrogastrography parameters | Patients       | Controls       |
|------------------------------------|----------------|----------------|
| DF (cpm)                           | 2.99±0.55      | 3.12±0.3       |
| DP (µV × µV)                       | 93225.19±184659.15 | 147460.6±144437.2 |
| Normogastria (%)                   | 62.11±18.71    | 87.14±9.02     |
| Bradygastria (%)                   | 8.92±7.21      | 2.78±4.09      |
| Tachygastria (%)                   | 8.9±7.06       | 4.86±4.48      |
| Arrhythmia (%)                     | 20.05±11.03    | 5.21±5.93      |

DF – dominant frequency; DP – dominant power of dominant frequency.
Table 9. Average slow wave coupling percentage.

| SWC (%) | Patients | Controls |
|---------|----------|----------|
| Fasted  | 55.99±9.46 | 77.44±11.89 |
| Fed     | 62.46±12.63 | 82.65±10.78 |

SWC – slow-wave coupling.

the plasma concentration of determined hormones. A presence of a very strong correlation (0.92) between the percentage of arrhythmia in the fasting EGG recording and ghrelin concentration was demonstrated. In the postprandial EGG recording, the correlation concerned ghrelin concentration and the tachygastria percentage (0.73). Both in the fasting and postprandial recording, a strong negative correlation was observed between plasma noradrenaline concentration and the average SWC percentage (–0.72).

DISCUSSION

Irritable bowel syndrome is characterized by pain in the abdominal cavity and irregularities in defecation. At present the main mechanism behind IBS is considered to be dysfunction of the brain-gut axis associated with disturbed motor activity of the digestive tract, visceral hypersensitivity and disturbed neuroimmunologic response of the intestines [19].

In 1928 a hypothesis was proposed that dysfunction of the autonomic nervous system could contribute to the manifestations observed in the course of IBS [11]. The ANS mediates communication between the brain and the digestive tract, and modulates and coordinates motor, secretory and immunologic functions of the digestive tract [20,21]. Increased sympathetic and decreased parasympathetic activity is an essential element of the body's response to stress. Stress and affective states cause sympathetic activation and therefore subsequent IBS manifestations [22]. Iovino et al. showed that activation of the sympathetic nervous system increased perception of intestinal wall stretching, which could explain the frequent complaints of pain and feeling of inflating intestines reported by IBS patients [23].

In recent years examinations estimating relations between the ANS activity and myoelectric activity of the stomach in IBS patients have not been conducted. HRV measurements and functional tests allowed us to demonstrate increased activation of the sympathetic part of the ANS and disturbed parasympathetic function in IBS-C patients, which is confirmed by Aggarwal et al, who described the presence parasympathetic dysfunction in IBS-C patients [15]. In our own examinations, HRV analysis in the DB test pointed to the dysfunction of the parasympathetic part of the ANS. Other researchers have observed low parasympathetic activity in the DB test, weakened sympathetic reply in the tilt test [24] and reduced parasympathetic response to stimulation with deep breathing in IBS-C patients [25]. We demonstrated abnormal results of the tilt test. Sympathetic predominance in the tilt test in IBS patients was also described in other studies [26,27]. Increased sympathetic activity was observed in women with IBS-C, and the diarrheal variant was associated with the opposite effect [28]. In a more recent survey, increased parasympathetic influences and reduced sympathetic/parasympathetic balance were observed in the diarrheal IBS form compared to constipation-predominant IBS [29]. However, a study done by Robert et al showed no difference in the autonomic activity between constipation- and diarrhoea-predominant IBS forms [30]; therefore, the authors proposed the hypothesis that there is a continuum of autonomous dysfunction in particular IBS subgroups. Recently, the degree of ANS dysfunction in IBS patients in terms of amount of increased sympathetic activity was confirmed by estimating blood flow in the finger tip by means of laser Doppler flowmetry [31].

In all examinations mentioned above, researchers used autonomic activity tests only. In order to confirm our results obtained in the ANS examinations plasma catecholamines concentrations were measured. The increased sympathet-ic activity was confirmed by the increased plasma catecholamines concentrations. Esler and Goulston demonstrated an increased urinary adrenaline concentration in patients with diarrheal-form IBS [32], and Heitkemper et al showed increased level of catecholamines and cortisol in urine in the course of IBS, but in this latter study only women were examined [33].

In IBS, disorders of the motor activity are observed on different levels of the gut, from the stomach to the colon. Regulatory peptides such as VIP, CCK or motilin influence the motor activity of the digestive tract. CCK participates in signal transduction in the brain-gut axis through the primary afferent fibres of the vagal nerve, and the same fibres probably demonstrate the expression of receptors for ghrelin [34]. Ghrelin stimulates the motor activity of the digestive tract, triggering MMC and fastening stomach emptying [35]. Apart from the vagal nerve, receptors for ghrelin can be found in the digestive tract muscular layer and in the CNS [35]. Depending on the place of release, regulatory peptides can act as hormones, neurotransmitters or neuro-modulators, and therefore they can play an important role in the pathogenesis of IBS manifestations such as abdominal pain, diarrhoea and constipation [36].

In the presented study decreased plasma ghrelin and CCK concentrations were noted. Meanwhile, Sjölund et al observed abnormally prolonged cholecystokinin secretion in response to the fat-rich test meal in IBS patients [37]. Mangel et al stated that the CCK application in healthy people can weaken colon motor activity, but it does not trigger the same effect in IBS-C patients [38]. The role of ghrelin in IBS pathology was studied by El-Salhy et al [39], who did not observe differences in the plasma ghrelin activity in comparison to the control group, but examining the density of cells having receptors for ghrelin in the stomach and the duodenum they stated that it was reduced in constipation-predominant IBS, and increased in the diarrheal form. Researchers explained that in order to compensate for increased or reduced density of ghrelin cells, the synthesis and release of ghrelin may be reduced in the diarrheal form and increased in the constipation form. With time this mechanism can run out, with subsequent increase in the synthesis and release of ghrelin in the diarrheal form and reduction in the constipation form, and it is responsible for manifestations dominating in particular IBS subtypes.
Abnormal, reduced plasma CCK and ghrelin concentration in IBS-C patients may impair functioning of the brain-gut axis and underlie disorders of the motor activity of the stomach, confirmed in the electrogastrography recordings.

IBS is associated with behavioural factors, and stress is an element in the pathogenesis of IBS manifestations. IBS patient subgroups differ in the awareness and intensity of somatic and psychological manifestations, with greater intensity of concerns appearing in constipation-predominant IBS [40]. Stress is associated with increased cortisol concentration, which results in insulin resistance with hyperinsulinemia [41-43], and insulin is a crucial factor activating the sympathetic part of the ANS [44]. Our results show a significantly increased insulin level in IBS-C patients. Eriksson et al measured C peptide concentration, which is known to correspond with the concentration of secreted insulin. Concentration of C peptide was slightly lower compared to the diarrheal form, yet higher than in the control group [40]. In the same study patients had increased concentration of cortisol compared to the diarrheal form and the control group, which shows the role of stress in triggering hyperinsulinemia and sympathetic activation [40]. Hyperinsulinemia in IBS-C patients not only can explain sympathetic overactivity, it may also explain the decrease in the motor activity of the stomach and intestines.

Finding a link between potential myoelectrical activity disorders and ANS dysfunction was the basic aim of this work. EGG can vicariously detect disorders of the motor activity of the stomach in IBS patients. In some examinations an increased tachygastria percentage was demonstrated, while reduced postprandial activity was found in others [45,46]. EGG recording disturbances were observed in patients with coexisting functional dyspepsia [45], but in a 24-hour recording other researchers were able to register reduced tachygastria percentage [47]. A characteristic reduction of the dominant power was also observed, suggesting that electrogastrography could be an additional diagnostic method in distinguishing IBS and functional dyspepsia.

Our own results clearly show smaller normogastria percentage in the patients group in fasting conditions, not increasing significantly after a meal. Fasting DP value was lower in the patients group, but it increased in the postprandial period. van de Vort et al observed the lack of postprandial EGG amplitude increase highly correlating with delayed emptying of the stomach [48]. In our own work, patients had significantly lower percentage of slow wave coupling (SWC), both in average value as well as for individual pairs of channels, which attests to the disturbed propagation of slow waves in the stomach. Moreover, the SWC percentage stayed in the significantly lower percentage of slow wave coupling (SWC), both in average value as well as for individual pairs of channels, which attests to the disturbed propagation of slow waves in the stomach. In some examinations an increased tachygastria percentage was demonstrated, while reduced postprandial activity was found in others [45,46]. EGG recording disturbances were observed in patients with coexisting functional dyspepsia [45], but in a 24-hour recording other researchers were able to register reduced tachygastria percentage [47]. A characteristic reduction of the dominant power was also observed, suggesting that electrogastrography could be an additional diagnostic method in distinguishing IBS and functional dyspepsia.

Disorders of the GMA described in our study may result from the lack of the sympathetic-parasympathetic balance. Increased plasma catecholamines and insulin concentrations confirm the existence of the dysfunction of the ANS. Current pathophysiological IBS models combine the influence of the central nervous system with the activity of the intestinal and autonomous nervous systems. Disorders of the ANS can influence myoelectrical activity, motor activity of the digestive tract, resting muscle tone and pain conducting. Within the brain-gut axis, the central sympathetic influence is most probably responsible for disorders of the stomach myoelectrical activity in IBS patients, both in fasting and postprandial conditions, causing delayed emptying of the stomach and dyspeptic complaints.

**Conclusions**

Based on results of different examinations conducted in our study, it appears that sympathetic overactivity and parasympathetic dysfunction are associated with constipation-predominant IBS. ANS activity measurement with HRV and functional tests was a valuable method of autonomic balance assessment. Autonomic balance can be directly connected with enteric nervous system activity. Results were confirmed with biochemical tests. However, further research on the association of the heart and gastro-enteric autonomic activity is necessary; examinations of the autonomic nervous system activity cannot be treated as the only diagnostic tool in patients with irritable bowel syndrome.

**Conflicts of interest**

The authors declare no conflicts of interest.

**References:**

1. Mertz HR: Irritable Bowel Syndrome. N Engl J Med, 2003; 349: 2136–46
2. Ferguson A, Sircus W, Eastwood MA: Frequency of ‘functional’ gastrointestinal disorders. Lancet, 1977; 2: 615–14
3. Mitchell CM, Drossman DA: Survey of the AGA membership relating to patients with functional gastrointestinal disorders. Gastroenterology, 1987; 92: 1292–84
4. Drossman DA: The functional gastrointestinal disorders and the Rome III process. Gastroenterology, 2006; 130: 1377–90
5. Vanner SJ, Depew WT, Paterson WG et al: Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. Am J Gastroenterol, 1999; 94: 2912–17
6. Tolliver IA, Herrera JL, DiPalma JA: Evaluation of patients who meet clinical criteria for irritable bowel syndrome. Am J Gastroenterol, 1994; 89: 176–78
7. Farthing MJG: Irritable bowel syndrome: new pharmaceutical approaches to treatment. Baillière’s Clinical Gastroenterol, 1999; 13: 461–71
8. Choy WD, Cash BD: Irritable bowel syndrome: Update on colonic neuromuscular dysfunction and treatment. Curr Gastroenterol Rep, 2006; 8: 273–81
9. Konturek SJ, Pawlik WW, Dajani EZ: Brain-gut axis in gastrointestinal system: introductory remarks. J Physiol Pharmacol, 2003; 54(Suppl.4): 3–7
10. Peters TL: Central and peripheral mechanisms by which ghrelin regulates gut motility. J Physiol Pharmacol, 2003; 54(Suppl.4): 95–103
11. Bockus HL, Bank J, Wilkinson SA: Neurogenic mucous colitis. Am J Med Sci, 1928; 176: 813–29
12. Fukudo S, Suzuki J: Colonic motility, autonomic function, and gastrointestinal hormones under psychological stress in irritable bowel syndrome. J Exp Med, 1987; 151: 373–85
13. Camilleri M, Fealey RD: Idiopathic autonomic denervation in eight patients presenting with functional gastrointestinal disease: a causal association? Dig Dis Sci, 1990; 35: 609–16
14. Smart HL, Atkinson M: Abnormal vagal function in irritable bowel syndrome. Lancet, 1987; 2: 475–78
15. Aggarwal A, Cutts TF, Abell TL et al: Predominant symptoms in irritable bowel syndrome correlate with specific autonomic nervous system abnormalities. Gastroenterology, 1994; 106: 945–50
16. Jorgensen LS, Christiansen P, Rasmadhul U et al: Autonomic nervous system function in patients with functional abdominal pain. An experimental study. Scand J Gastroenterol, 1993; 28: 63–68
17. Khurana RK, Nicholas EM: Head-up tilt table test: how far and how long? Clin Auton Res, 1996; 6: 335–41
18. Khurana RK, Setty A: The value of the isometric hand-grip test–studies in various autonomic disorders. Clin Auton Res, 1996; 6: 211–18
19. Harris L: Irritable Bowel Syndrome – Advances in Diagnosis, Pathophysiology, and Treatment. Business Briefing: Women’s Healthcare, 2004: 89–97
20. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES: The sympathetic nerve – an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev, 2000; 52: 595–638
21. Hansen MB: The enteric nervous system I: organisation and classification. Pharmacol Toxicol, 2003; 92: 105–13
22. Manabe N, Tanaka T, Hata J et al: Pathophysiology underlying irritable bowel syndrome – from the viewpoint of dysfunction of autonomc nervous system activity. J Smooth Muscle Res, 2009: 45: 13–23
23. Iovino P, Arpiro F, Domingo E, Malagelada JR: The sympathetic nervous system modulates perception and reflex responses to gut distention in humans. Gastroenterology, 1995; 108: 680–86
24. Adeyemi EO, Desai KD, Towsey M, Ghista D: Characterization of autonomic dysfunction in patients with irritable bowel syndrome by means of heart rate variability studies. Am J Gastroenterol, 1999; 94: 816–23
25. Lee CT, Chuang TY, Lu CL et al: Abnormal vagal cholinergic function and psychological behaviors in irritable bowel syndrome patients: a hospital-based Oriental study. Dig Dis Sci, 1998; 43: 1794–99
26. Heitkemper M, Jarrett M, Cain KC et al: Increased urine catecholamines and cortisol in women with irritable bowel syndrome. Am J Gastroenterol, 1996; 91: 906–13
27. Jorgensen LS, Christiansen P, Raundahl U et al: Autonomic nervous system function in patients with functional abdominal pain. An experimental study. Scand J Gastroenterol, 1993; 28: 63–68
28. Dockray GJ: Luminal sensing in the gut: an overview. J Physiol Pharmacol, 2003; 54(Suppl.4): 9–17
29. Peeters TL: Central and peripheral mechanisms by which ghrelin regulates gut motility. J Physiol Pharmacol, 2003; 54(Suppl.4): 95–103
30. Morise K, Furusawa A, Yamamoto H, Saito H: [Role of gut hormones in irritable bowel syndrome]. Nippon Rinsho, 1992; 50: 2697–702
31. Tanaka T, Manabe N, Hata J et al: Characterization of autonomic dysfunctions in symptom subgroups of women with irritable bowel syndrome. Am J Gastroenterol, 1996; 91: 110–14
32. Mangel AW, Brazer SR, Smith JW et al: Inhibition of colonic motility by ghrelin in patients with irritable bowel syndrome. Scand J Gastroenterol, 1996; 31: 110–14
33. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES: The sympathetic nerve – an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev, 2000; 52: 595–638
34. Adeyemi EO, Desai KD, Towsey M, Ghista D: Characterization of autonomic dysfunction in patients with irritable bowel syndrome by means of heart rate variability studies. Am J Gastroenterol, 1999; 94: 816–23
35. Lee CT, Chuang TY, Lu CL et al: Abnormal vagal cholinergic function and psychological behaviors in irritable bowel syndrome patients: a hospital-based Oriental study. Dig Dis Sci, 1998; 43: 1794–99
36. Heitkemper M, Jarrett M, Cain KC et al: Increased urine catecholamines and cortisol in women with irritable bowel syndrome. Am J Gastroenterol, 1996; 91: 906–13
37. Dockray GJ: Luminal sensing in the gut: an overview. J Physiol Pharmacol, 2003; 54(Suppl.4): 9–17
38. Peeters TL: Central and peripheral mechanisms by which ghrelin regulates gut motility. J Physiol Pharmacol, 2003; 54(Suppl.4): 95–103
39. Morise K, Furusawa A, Yamamoto H, Saito H: [Role of gut hormones in irritable bowel syndrome]. Nippon Rinsho, 1992; 50: 2697–702
40. Mangel AW, Brazer SR, Smith JW et al: Inhibition of colonic motility by ghrelin in patients with irritable bowel syndrome. Scand J Gastroenterol, 1996; 31: 110–14
41. Ely DL: Organization of cardiovascular and neurohumoral responses to stress. Implications for health and disease. Ann NY Acad Sci, 1995; 771: 594–608
42. Young EA, Abelson J, Lightman SL: Cortisol pulsatility and its role in stress regulation and health. Front Neuroendocrinol, 2004; 25: 99–76
43. Reinehr T, Andler W: Cortisol and its relation to insulin resistance before and after weight loss in obese children. Horm Res, 2004; 62: 107–12
44. Landsberg L: Insulin resistance, energy balance and sympathetic nervous system activity. Clin Exp Hyperins. A, 1996; 12: 817–30
45. Lealh A, Besherdas K, Clayman C et al: Abnormalities of the electrogastrogram in functional gastrointestinal disorders. Am J Gastroenterol, 1999; 94: 1023–28
46. Lin X, Levanon D, Chen JD: Impaired postprandial gastric slow waves in patients with functional dyspepsia. Dig Dis Sci, 1998; 43: 1678–84
47. Hocke M, Seidel T, Sprott H et al: Ambulatory electrogastrography in patients with scleroderma, delayed gastric emptying, dyspepsia, and irritable bowel syndrome. Is there any clinical relevance? Eur J Intern Med, 2001; 12: 366–71
48. van der Voort IR, Osmanoglou E, Seybold M et al: Electrogastrography and cortisol in women with irritable bowel syndrome. Int J Mol Med, 2009; 23: 703–7
49. Eriksson EM, Andreen KI, Eriksson HT, Karlberg GK: Irritable bowel syndrome subtypes differ in body awareness, psychological symptoms and biochemical stress markers. World J Gastroenterol, 2008; 14: 4889–96
50. Evans PR, Bak YT, Shuter B et al: Gastroparesis and small bowel dysmotility in irritable bowel syndrome. Dig Dis Sci, 1997; 42: 2087–93