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### Improvement of Meal-Induced Gastric Compliance and Gastric Emptying in Patients with Functional Dyspepsia By Treatment with Rikkunshito (Liu-Jin-Zi-Tang: Traditional Chinese Herbal Medicine).—Real-Time Ultrasonographic Study—

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**Background:** Some patients with functional dyspepsia present with impaired gastric compliance and gastrointestinal motility. A traditional Chinese herbal medicine, Rikkunshito (Chinese name Liu-Jin-Zi-Tang), has been identified as an effective drug against dyspeptic symptoms and is widely used for therapy in patients with functional dyspepsia (FD). In this study, we examined the effect of this drug on gastric compliance and gastrointestinal motility in FD patients. **Methods:** Ten patients with FD (mean age, 50.8 years) were studied ultrasonographically, before and after 14 days of treatment with Rikkunshito (7.5g b.d.). For assessment of gastric compliance, a cross-sectional area of the proximal stomach was measured after stepwise incremental ingestion of a liquid meal (consomme soup: 3.25 kcal/100 ml) up to a total of 400 ml. We used percent change (area after ingestion of each volume-area before ingestion) $\times$ 100/area before ingestion as the parameter of compliance of the proximal stomach. Then, gastric emptying, antral contractions and duodenogastric reflux (DGR) were observed using previously reported methods (Scand J Gastroenterol 1994; 29:897-902, J Gastroenterol Hepatol 2000; 15:1022-1027, Gut 2002; 51:A188). Each parameter was calculated as follows: gastric emptying rate=(antral area at 1 min-area at 15 min) $\times$ 100/antral area at 1 min, motility index (MI)=number of antral contractions for 3 min $\times$ (area relaxed-area contracted) $\times$ 100/area relaxed, reflux index (RI)=no. of DGR events for 5 min $\times$ length of reflux signal detected by color Doppler. **Result:** Symptom scores after treatment decreased significantly. The percent change of the cross-sectional area of the proximal stomach was significantly greater after treatment with Rikkunshito than that before treatment (before treatment vs after treatment: 4.63 vs 6.07,  $p=0.028$  after 300 ml ingestion, 5.81 vs 10.94,  $p=0.028$  after 400 ml ingestion). Although, gastric emptying rate increased significantly (53.95 vs 68.87,  $p=0.045$ ), there were no significant differences in the MI and RI before and after treatment with Rikkunshito (MI: 7.96 vs 8.71,  $p=0.244$ , RI: 18 vs 18,  $p=0.957$ ). **Conclusion:** Rikkunshito enhanced meal-induced gastric compliance and gastric emptying rate. This observation suggests that Rikkunshito may be beneficial for FD patients with impaired gastric compliance and delayed gastric emptying.

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### Effect of Bifidogenic Growth Stimulator On Patients with Constipation-Predominant Irritable Bowel Syndrome

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**Background and Aim:** One of the pathogenesis of irritable bowel syndrome (IBS) has been postulated to be a deranged intestinal microflora. Bifidogenic growth stimulator (BGS), 1,4-dihydroxy-2-naphthoic acid, is a product by propionic acid bacteria and has been shown to increase in the number of intestinal bifidobacteria selectively. This product has been approved and is commercially available in Japan. A number of studies have shown that probiotics such as bifidobacterium and lactobacillus improve the symptoms in patients with IBS, however, the efficacy of prebiotics on IBS has not been examined. We evaluated the effect of BGS on patients with constipation-predominant IBS. **Methods:** Twelve patients with constipation-predominant IBS (Rome III criteria) were enrolled (male 3, female 9, age 27-77). Study was performed in double-blind crossover fashion. Patients received BGS 4.5g or placebo orally for 4 weeks, followed by 4 weeks of washout period, then received placebo or BGS for 4 weeks (total 12 weeks). 1) Number of bowel movement, 2) stool forms (Bristol scale), 3) abdominal pain, 4) abdominal bloating, 5) incomplete evacuation, and 6) overall symptoms, were recorded by the patients in diary every day (3-6: visual analogue scale). SF-36 was used to assess the QOL in each pre and post prescribing periods (total 4 times). Overall impression was also asked as "which period was better in your symptoms?" in the end of study. Each symptom was evaluated from day 15 to day 28. The differences of SF-36 score in each pre and post period were also evaluated. **Results:** Incomplete evacuation (placebo vs BGS: VAS 5.15  $\pm$  2.29 vs 4.08  $\pm$  2.33,  $p=0.008$ ), and overall symptoms (5.22  $\pm$  1.10 vs 4.57  $\pm$  1.01,  $p=0.038$ ) were significantly improved. Abdominal bloating (5.64  $\pm$  1.98 vs 4.72  $\pm$  2.18,  $p=0.089$ ) and bowel movement (0.82  $\pm$  0.48 vs 1.09  $\pm$  0.88,  $p=0.082$ ) were not significant but improved. In SF-36, body pain was significantly decreased (change scores: +1 vs +8,  $p<0.05$ ). In overall impression, the number of patients who were favor in BGS was 8 out of 12. **Discussion:** This study showed that prebiotics improved several symptoms in patients with constipation-predominant IBS. Side effects of prebiotics seem to be less than any other drugs and probiotics. In a certain group of IBS, prebiotics would be one of the option for treatment. **Conclusion:** BGS as prebiotics was effective in patients with constipation-predominant IBS.

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### Influence of Itopride On Gastrointestinal Motility in Dyspeptic Patients.—Real-Time Ultrasonographic Study—

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**Background:** Itopride is a prokinetic agent which has anti-dopaminergic and anti-acetylcholine esterase activities. An important placebo-controlled trial reported that itopride was effective for the symptoms of functional dyspepsia (FD), but its effects on gastrointestinal motility have not been fully studied. The aim of the present study was to determine the influence of itopride on gastrointestinal motility in FD patients. **Methods:** Eighteen patients with FD (mean age, 42.0 years) were studied ultrasonographically, before and after 14 days of treatment with itopride (150 mg b.d.). For assessment of gastric compliance, a cross-sectional area of the proximal stomach was measured after stepwise ingestion of a liquid

meal (consomme soup: 3.25 kcal/100 ml), up to 400 ml. Then, gastric emptying, antral contractions and duodenogastric reflux (DGR) were observed using previously reported methods (Scand J Gastroenterol 1994; 29:897-902, J Gastroenterol Hepatol 2000; 15:1022-1027, Gut 2002; 51:A188). Each parameter was calculated as follows: % gastric emptying=(antral area at 1 min-area at 15 min) $\times$ 100/antral area at 1 min, motility index=number of antral contractions for 3 min $\times$ (area relaxed-area contracted) $\times$ 100/area relaxed, reflux index=no. of reflux events for 5 min $\times$ length of reflux signal detected by color Doppler. **Result:** Symptom scores after treatment decreased significantly. There were no significant differences in % gastric emptying, MI, and DGR before and after treatment with itopride (% gastric emptying: 54.6 vs 56.1, motility index: 9.01 vs 8.90, DGR: 29 vs 25). Although the cross-sectional area of the proximal stomach after the ingestion of 300 ml (27.3 vs 29.2 cm<sup>2</sup>,  $p=0.072$ ) and 400 ml (33.2 vs 35.5 cm<sup>2</sup>,  $p=0.072$ ) of the liquid meal tended to be larger after treatment with itopride than that before the treatment, there were no statistically significant differences. **Conclusion:** This medicine improved dyspeptic symptoms significantly, but there were few effects on gastrointestinal motor function. It is thought that this phenomenon occurred because the pharmaceutical doses used were low. However, this observation suggests that itopride may be beneficial for FD patients with impaired gastric compliance and delayed gastric emptying.

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### Sex Differences in Regional Functional Brain Activation Elicited By Colorectal Distention in Conscious, Non-Restrained Rats

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**BACKGROUND & AIMS:** Chronic abdominal pain syndromes are more common in women, and sex related differences in pain responses and in analgesic effectiveness have been demonstrated. We have previously demonstrated greater activation of central arousal circuits (including amygdala) in female IBS patients compared to male patients (Gastroenterol, 124:1738-47, 2003). Our aim was to identify possible sex differences in functional brain activation in response to noxious visceral stimulation (CRD) in conscious, unrestrained rats. **METHODS:** Female rats were implanted with telemetry transmitters for abdominal electromyographic (EMG) recording, and cannulated for cerebral perfusion mapping with [<sup>14</sup>C]-iodoantipyrine. Tracer was injected 35 s after the onset of CRD (barostat 60 mm Hg inflation of a 5-cm colorectal balloon,  $n=11$ ), followed by rapid euthanasia. Balloons in control rats remained un-inflated (0 mmHg,  $n=11$ ). EMG activity was analyzed as normalized area under the curve. Behavioral responses were scored as the percentage of time spent in postures indicative of visceral pain (e.g. arching). Brains were serially sectioned and autoradiographic images were digitized and used to reconstruct 3-dimensional brains. Regional cerebral blood flow related tissue radioactivity (rCBF-TR) was analyzed with statistical parametric mapping (SPM). Results were compared to those reported earlier by our group in male rats ( $n=24$ ) (Soc.Neurosci #724.14, 2007). **RESULTS:** CRD in males triggered significant bilateral activation of the dorsal aspect of cingulate, anterior insular, prelimbic, and primary somatosensory cortices, as well as the amygdala and caudate putamen. CRD in females, overall showed a similar pattern of activation as in males. However, in females, greater activation of the amygdala was observed, but no activation of the prelimbic and cingulate cortices. Females compared to males showed a trend toward greater EMG responses to 60-mmHg CRD (307  $\pm$  34% vs. 267  $\pm$  24%), with no sex differences in response to 0-mmHg CRD (103  $\pm$  27% vs. 103  $\pm$  8%), and a trend toward greater pain scores both to 60-mmHg CRD (89  $\pm$  5% vs. 77  $\pm$  6%), as well as to 0-mmHg CRD (12.5  $\pm$  3% vs. 3  $\pm$  3%). **CONCLUSION:** Our results demonstrate sex related differences in functional brain activation, behavioral and EMG responses to CRD in conscious, unrestrained rats. Similar to our previous findings in humans, the observed reduced activation of prelimbic and cingulate cortex and increased activation of the amygdala in female rats suggests the possibility of sex related differences in the inhibitory control of the amygdala by medial prefrontal cortex.

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### Assessment of Colonic Secretory Function and Faecal Output in Viscerally Hypersensitive Wistar Kyoto Rats

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**Introduction:** Anxiety-prone Wistar Kyoto (WKY) rats display increased visceral hypersensitivity following colorectal distension (CRD) and altered brain-gut axis function relative to normo- or hypo-sensitive rat strains (Gibney et al., 2007; Gunter et al., 2000). Thus the WKY strain may be a useful animal model of irritable bowel syndrome (IBS). To date, few studies have investigated colonic function in WKY rats which may contribute to functional symptoms of IBS for example, diarrhoea and constipation. **Aims & Background:** Our aim was to assess visceral hypersensitivity and faecal output during open field (OF) stress in WKY and Sprague Dawley (SD) rats. Colonic ion transport was assessed in Ussing chambers. **Methods:** Male rats were exposed to CRD (40mmHg; 10mins) and abdominal contractions counted or to OF stress (10mins) during which faecal output was monitored. Mucosal tissues from WKY and SD rats were placed in Ussing chambers and voltage-clamped at 0mV. Veratridine (30 $\mu$ M) or capsaicin (3 $\mu$ M) were added to stimulate submucosal nerves. Bethanechol (BCh, 100 $\mu$ M) and forskolin (10 $\mu$ M) were added +/- tetrodotoxin (TTX, 300nM) to assess Ca<sup>2+</sup>- and cAMP-stimulated changes in short circuit current (I<sub>sc</sub>). **Results:** WKY animals displayed increased abdominal contractions compared to SD rats during CRD (WKY, 12.1 $\pm$ 1.3 ( $n=14$ ); SD, 7.9 $\pm$ 0.9 ( $n=14$ ),  $P<0.05$ ). Moreover, during OF stress WKY animals expelled significantly more faecal pellets (WKY, 3.8 $\pm$ 0.7 ( $n=10$ ); SD, 1.7 $\pm$ 0.6 ( $n=10$ ),  $P<0.05$ ). Basal I<sub>sc</sub> was significantly decreased in WKY compared SD tissues (WKY, 39.1 $\pm$ 4.1 $\mu$ A.cm-2 ( $n=4$ ); SD, 63.8 $\pm$ 5.0 $\mu$ A.cm-2 ( $n=4$ ),  $P<0.01$ ). Transepithelial resistance was comparable between strains. Veratridine-stimulated responses were unaltered in WKY tissues (WKY, 33.1 $\pm$ 2.0 $\mu$ A.cm-2 ( $n=4$ ); SD, 32.4 $\pm$ 3.6 $\mu$ A.cm-2 ( $n=4$ )); as was the case for capsaicin-induced changes in I<sub>sc</sub>. Biphasic BCh responses were insensitive to TTX pre-treatment, and were significantly decreased in WKY colon (WKY I, 6.6 $\pm$ 2.3 $\mu$ A.cm-2 ( $n=4$ ), WKY II, 17.9 $\pm$ 6.6 $\mu$ A.cm-2 ( $n=4$ ); SD I, 34.2 $\pm$ 5.1 $\mu$ A.cm-2 ( $n=4$ ), SD II, 112.3 $\pm$ 9.4 $\mu$ A.cm-2, ( $n=4$ )  $P<0.01$  and  $P<0.001$ ). cAMP-induced secretory responses were unchanged in the WKY