Delayed parasympathetic recovery from a psychological stimulus in female college students with gastrointestinal symptoms

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Abstract

It is well known that mental stress often induces gastrointestinal (GI) symptoms, such as abdominal pain, nausea and diarrhea. Irritable bowel syndrome (IBS) is one of the most common diseases, characterized by abdominal pain associated with altered bowel habit, such as diarrhea, constipation or both. Abnormality in brain-gut axis, autonomic dysregulation, visceral hypersensitivity, or altered emotional processing is considered to be the important contributing factor in the pathogenesis of IBS. However, precise pathophysiology of IBS is still complex and not completely understood. To clarify the role of reactivity to stress in the pathogenesis of IBS, characteristics of autonomic responses to physical (cold pressor test) and psychological (Stroop color-word conflict test) stimuli were examined, along with the mood change associated with the stimuli, in female college students with gastrointestinal symptoms (who met Rome III criteria for IBS, without checkup for gastrointestinal organic diseases). Mood states were estimated by a profile of mood states, and autonomic nervous function was evaluated by a spectral analysis of heart rate variability (HRV), baroreflex sensitivity, and systolic and diastolic blood pressure. Repeated measures analysis of variance (ANOVA) revealed significant interaction of group (females with GI symptoms and healthy controls) × time course after the psychological stimulus in HF amplitude of HRV, that is, delayed and attenuated recovery after the Stroop color-word conflict test in females with GI symptoms. Repeated measures ANOVA also revealed significant main effect of group in baroreflex sensitivity, that is, the baroreflex sensitivity is generally lower in females with GI symptoms, though the time courses in both groups were similar. Prestimulus basal level of tension-anxiety were significantly higher in females with GI symptoms compared to controls. These results suggest that attenuated and delayed recovery from psychological stimuli may indicate altered emotional processing which could contribute to various gastrointestinal and psychological symptoms.

Keywords: Irritable bowel syndrome, heart rate variability, profile of mood states, cold pressor test, stroop color-word conflict test

Introduction

In recent years, a large number of people in advanced countries are exposed to various psychosocial stressors in their complicated daily lives. These stressors are believed to contribute highly to the pathogenesis and development of some psychosomatic disorders. Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal (GI) disorder, defined as a chronic continuous or remittent disorder characterized by abdominal discomfort or pain combined with altered bowel

habits, diarrhea, constipation or alteration of both, and associated with stress, depression, anxiety, tension, or previous intestinal infection [1]. Abnormal brain-gut interaction [2,3], altered emotional processing [4], gastrointestinal motility and secretion disorder [5-7], autonomic nervous dysfunction [8-11], visceral hypersensitivity [12-14], or altered CRF signaling [15-17], which are supposed to be at least partially attributable to some kind of stress, are considered to play an important role in the pathogenesis of IBS. However, precise pathophysiology of IBS

is still complex and not completely understood.

Gastrointestinal tract has an automaticity and is regulated appropriately by parasympathetic nervous tone. Therefore, parasympathetic withdrawal was supposed to induce gastrointestinal dysregulation, which could consequently allow disordered bowel movements or secretions, and may cause various abdominal symptoms. IBS could often be triggered by or worsen with psychological stress which provokes anxiety and/or tension. Psychological stress generally induces sympathetic activation and parasympathetic withdrawal, along with HPA (hypothalamic-pituitary adrenal) axis activation. The increased sympathetic nervous activity and decreased parasympathetic nervous activity are considered to be the major cause in male patients with IBS [9,11]. On the other hand, there are various conflicting reports about the activities of both autonomic branches in female patients with IBS, and visceral hypersensitivity is believed to have some correlation with the generation or maintenance of IBS in female patients [8,13]. Altered HPA axis activity is suggested to contribute to the pathophysiology of IBS through enhanced CRF (corticotropin releasing factor) effects on gastrointestinal tracts [15-17]. Since IBS is considered to be a stress related non-organic disease, patients with IBS may react with stress in a different manner from healthy individuals. According to Lazarus and Folkman [18], there supposed to be 3 levels of stress: psychological, physiological and social aspects. A physiological stress induce fight or flight response to help organisms to survive immediate danger, whereas psychological stress requires cognitive processes to determine whether an event is perceived as being stressful or not. Social stressors like difficulty in human relationship, high demands of study, or anxiety for future, can affect stress related systems, but not easily applied in laboratory experimental settings. There are a number of studies which have investigated the acute stress response in IBS [19-22], however, precise roles of reactivity to stress in pathophysiology of IBS are not fully understood.

The purpose of this study was to examine the role of reactivity to stress in the development of IBS.

Therefore, the responses of autonomic nervous system and mood to physical and psychological stimuli were examined to clarify the response characteristic in females with various abdominal symptoms (who met Rome III criteria for IBS). Cold pressor test is a test to examine autonomic nervous function by immersing a hand in ice water for a while, and is thought to generally elicit sympathetic activation [23]. Stroop color-word conflict test (Stroop test) is a widely used test which was originally designed to investigate cognitive function in frontal lobe, and frequently used as a psychological stimulus in various experimental settings [24,25]. We applied Cold pressor test and Stroop test as a physical stimulus and a psychological stimulus, respectively.

Autonomic nervous responses were evaluated by responses of heart rate variability (HRV), baroreflex sensitivity, and systolic and diastolic blood pressure (BP) to the stimuli, and mood changes were evaluated by Profile of Mood States (POMS).

Methods

Subjects

The study was approved by The Ethics Committee at our university before hand. Potential participants were selected from 18 to 22 years old female college students according to Rome III criteria [26]. Since exclusion diagnosis with blood, stool, and endoscopic examinations were not performed, those candidates who met the criteria for IBS were defined as subjects with gastrointestinal symptoms (GI subjects), and those who did not meet the criteria at all as healthy controls. Fifteen GI subjects (mean age 21.07 years, range 19-22) and 10 controls (mean age 21 years, range 19-22) participated in the study after providing written informed consents in accordance with the Declaration of Helsinki. Education, nationality, and ethnicity along with gender and age were matched since all subjects were female Japanese students recruited from our college.

Experiment days were planned on the third day of menses or later in their follicular phase to minimize the effects of menstrual cycle on mood and autonomic nervous system [27,28].

The day and time of the experiments were counter balanced between each subject group in the aspects of the time zone and of the day of week, to minimize circadian rhythm effects on mood and autonomic nervous system [29]. They were asked to abstain from eating, and drinking for at least 3 hours before the experiment, and to sleep for more than 6 hours on the previous night. Strenuous exercise, heavy drink and taking medicine on the previous day were also prohibited. The menstrual phase was determined by the onset of next menses, and 3 GI subjects and 2 controls were excluded from the analysis because their experiments were considered to be performed in their luteal phase. Autonomic data were partially missed due to recording problems in 2 controls, then, these data were excluded for the analysis of autonomic indices.

Study procedures

The experimental procedure is shown in **Figure 1**. The subjects entered the room and were asked to fill out POMS questionnaires for an evaluation of their basal mood state. Each subject sat up right on a chair while disc electrodes were attached for chest electrocardiograms (ECG) with CM5 leads, and a thermistor was attached just under one nostril for detecting respiration. A tonometric sensor was attached on a radial artery to measure blood pressure (BP) with the tonometric method (JENTOW, Japan). ECG, BP, and respiration curves were recorded during the 10-minute pre-stimulus basal period, the physical stimulus period of one minute, 15 minute recovery phase after the 1st stimulus, and the psychological stimulus period of 5 minutes, a post-stimulus POMS period of a few minutes, and 15 minute recovery phase after the 2nd stimulus. The stimuli were presented in fixed order. Data were stored on a personal computer equipped with a 12-bit analog-digital converter (ADTM-98, Canopus, Kobe, Japan) for subsequent offline analysis with a sampling frequency of 1kHz. Each recovery phase was divided into three 5-minute epochs and named rest 1, 2, 3 and rest 4, 5, 6 for later analysis.

Subjects were asked to keep quiet, avoiding any disruptive movements of their heads or hands throughout the experiments. They were also asked to keep their eyes closed but not to fall asleep during the recovery phases. Immediately after accomplishing the Stroop test they were asked to fill out POMS questionnaires for an evaluation of whatever mood states were induced by the stimulus.

POMS data were summed to generate six sub-scales: T-A (tension and anxiety), D (depression and dejection), A-H (anger and hostility), V (vigor), F (fatigue) and C (confusion). These summed raw scores were converted into T-scores for parametric statistical analysis according to the POMS manual [30].

Subjects were exposed to cold pressor test by immersing a hand up to the wrist in cold water (4 ± 1 degree centigrade) for 1 min. The room temperature was kept at 22 ± 2 degree centigrade by an air conditioner.

Computerized Stroop test (made with SuperLab 4.5, Cedrus corporation, USA) was applied by presenting color name words (blue, green, yellow, red and black) in a color which was either congruent or incongruent with the name on a PC display. Subjects were asked to push “Y” button in case the color name coincides with the color, and push “N” button in the other case. Three hundred sixty color name words were presented randomly. They were instructed to perform the test as accurately and quickly as possible.

Data acquisition and analysis

HRV analyses

ECG data were digitized at a sampling frequency of 1 kHz on a personal computer. After detecting every R-wave peak, consecutive R-R intervals on the ECG were calculated, excluding ectopic beats and abrupt discharges in R-R intervals. Spectral analysis was applied to the time series data of R-R intervals for each epoch, using the maximum-entropy method (MemCalc Version 2.5, Suwa Trust) [31]. After calculating the power-spectral density, the magnitude of the power for HRV was obtained by measuring areas under the spectral density curves. The values were divided into two major bands, a low-frequency component (LF; 0.04-0.15 Hz) and a high-frequency component (HF; 0.15-0.4 Hz). Thereafter, the amplitude of each frequency band was calculated as twice the power magnitude and the square root

thereof. It is known that the HF corresponds to respiratory sinus arrhythmia (RSA) and reflects parasympathetic nerve activity, and the LF corresponds to Mayer-wave-related sinus arrhythmia and relates to both sympathetic and parasympathetic nerve activities [32-36]. Then HF amplitude (HF) was considered as an index of parasympathetic nervous function and LF/HF amplitude (LF/HF) as a marker of relative sympathetic activity [29,34].

BP wave forms were digitized at a sampling frequency of 1 kHz on a personal computer. Beat-to-beat systolic and diastolic peaks of the BP wave were detected and stored as time series data of systolic BP and diastolic BP, respectively. Spectral analysis was applied to the time series data of systolic BP for each epoch, then LF and HF amplitudes of systolic BP variability were obtained in the same way as the spectral analysis of HRV. Thereafter, baroreflex sensitivity was calculated as the ratio of LF amplitude of HRV to LF amplitude of systolic BP variability (msec/mmHg). Mean systolic BP and diastolic BP were also calculated for every epoch.

For physiological data analysis, five-minute data just prior to the stimulus period were used to establish pre-stimulus basal activity (basal), and 15-minute data for the recovery phase were divided into 3 five-minute epochs and represented as rest 1, 2, 3, 4, 5 and 6. Response to the stimuli and recovery from the stimuli, as well as whole trend, were analyzed separately, since there may be some differences between response and recovery.

Statistical analysis

To clarify the characteristics of autonomic responses to physical and psychological stimuli in females with GI symptoms, interactions between group (GI subjects and control: between-subjects variable) and entire time course (before and after the stimuli: within-subjects variable) of each index were examined by repeated measures analysis of variance (ANOVA). A repeated measures ANOVA is referred to as a within-subjects ANOVA and is suitable to investigate changes in values over time from the same participants, and can examine the difference of trend of values among groups. Furthermore, to clarify the difference of response pattern, repeated measures ANOVA were applied to the autonomic responses to, and recoveries from physical and psychological stimuli in both groups. Student's *t*-test was applied to clarify the difference of basal value in each subscale

of POMS. Pearson's correlation coefficients were also calculated between basal score of T-A subscale in POMS and autonomic indices to elucidate contributing factors to basal T-A elevation which was shown in GI subjects. Effect size (partial η^2 for repeated measures ANOVA, Cohen's d for student's t -test) was also calculated to help readers fully understand the importance of the findings in the study [37-39]. Statistical analysis was performed on a personal computer using Statview Ver. 5.0 (HULINKS), and differences with a probability value of less than 0.05 were considered significant.

Results

Autonomic nervous system

There was no significant interaction or main effect of group in whole trend, response to the stimuli, and recovery from the stimuli of LF/HF amplitude, diastolic BP, and systolic BP. Whole trend of HF amplitude seems lower in GI subjects than in controls, though there was no significant interaction or main effect of group in the whole trend (Figure 2). Significant group $\times$ recovery interaction was seen only in the recovery phase of HF amplitude from Stroop test ($F(2,32)=4.678$, $p=0.0165$, partial $\eta^2=0.226$) (Figure 3). Recovery after the Stroop test was prompt and approached closely to the pre-stimulus level in control group, but the recovery was slow and little in GI subjects. There was significant main effect of group in whole trend of baroreflex sensitivity ($F(8,128)=5.126$, $p<0.0001$, partial $\eta^2=0.243$), that is, the values were generally lower in GI subjects compared to those in controls (Figure 4).

Mood

Of 6 subscales of POMS, only T-A showed significant group $\times$ mood response interaction ($F(1,18)=4.981$, $p=0.0386$, partial $\eta^2=0.217$), that is, T-A increased after the stimuli in control, but not in GI subjects (Figure 5). Pre-stimulus basal value of T-A was significantly higher in GI subjects ($M=52.301$, $SD=8.992$, $n=12$) than control ($M=44.035$, $SD=6.519$, $n=8$) (t -test, $p=0.0387$) with a large sized effect (Cohen's $d=1.073$). Pre-stimulus basal value

of the other subscales were not significantly different between GI subjects and controls. No significant correlation was found

Figure 3. Recovery from physical (cold pressor test) and psychological (Stroop test) stimuli of HF amplitude in each group. Closed square: in subjects with gastrointestinal symptoms (GI subjects), open circle: in controls. Repeated measures ANOVA showed no significant group $\times$ time course interaction in recovery from the physical stimulus, but significant group $\times$ time course interaction in recovery from the psychological stimulus ($F(2,32)=4.678$, $p=0.0165$).

Figure 4. Time course of baroreflex sensitivity in each group. Closed square: in subjects with gastrointestinal symptoms (GI subjects), open circle: in controls. Repeated measures ANOVA showed significant main effect of group ($F(1,16)=5.118$, $p=0.038$), but showed no significant group $\times$ time course interaction.

Figure 2. Time course of HF amplitude in each group. Closed square: in subjects with gastrointestinal symptoms (GI subjects), open circle: in controls. No significant group $\times$ time course interaction was shown by repeated measures ANOVA.

between basal score of T-A subscale in POMS and autonomic indices.

Discussion

Though the prevalence of IBS varies among countries, the overall prevalence is supposed to be approximately 10% to 15% [40,41], which is much higher than that of inflammatory bowel disease, such as Crohn's disease, and ulcerative colitis. Prevalence of inflammatory bowel disease, is estimated about 0.1% [42]. Ishihara et al., reported the prevalence of organic colonic diseases in patients who met the Rome III criteria to be approximately 10% and indicated that the Rome III criteria were

Figure 5. T-scores of six sub-scales of POMS in each group. Closed square: scores in subjects with gastrointestinal symptoms (GI subjects), open circle: scores in controls. Significant group (GI subjects and control)×time course (pre- and post-stimuli) interactions were shown only in T-A ($F(1,18)=4.981, p=0.0386$) as indicated by asterisks. T-A: Tension-Anxiety; D: Depression-Dejection; A-H: Anger-Hostility; V: Vigor; F: Fatigue; C: Confusion; *denotes $p<0.05$, revealed by t -test.

adequately specific for the diagnosis of IBS without performing a colonoscopy examination [43]. Taken together, most of the GI subjects in this study who met the Rome III criteria for IBS would presumably be with IBS and without organic disorders, though there might be a little possibility that a few subjects with organic bowel disease may have been included.

The lowered trend of baroreflex sensitivity in GI subjects may indicate that the baroreflex sensitivity was usually decreased in IBS patients. Baroreflex sensitivity is thought to decrease under tension or stressful environment, and said to be low in patient with hypertension [44,45]. Since no significant interaction or main effect of group was observed in systolic and diastolic BP, tension or stress would have caused the decrease of baroreflex sensitivity. Spaziani et al., also reported lowered baroreflex sensitivity in patients with IBS, though the precise mechanism was not detailed [46]. Significantly higher basal score of T-A in GI subjects would also support that tension and/or stress induced anxiety might have caused the decrease of baroreflex sensitivity in GI subjects. Or lowered baroreflex sensitivity may be one of the characteristics of autonomic nervous system in IBS.

Significantly higher basal score of T-A may indicate that tension and/or anxiety would have accumulated close to the ceiling level in GI subjects, which could subsequently result in relatively less response to the stimuli. Bengtsson et al., previously described higher anxiety in patients with IBS compared to patients with inflammatory bowel diseases [47], which is consistent with this finding.

Since the other 5 subscales of POMS showed no significant interaction or main effect of group, tension and anxiety may be the emotion which is associated most with stress responses. Corticotropin-releasing factor (CRF) is a well-known mediator which is released when exposed to various stressors, and is described to play an important role in both gut motility modulation and anxiety induction during stress [15-17]. Then it is plausible that stressors may induce gut motility alteration and anxiety via HPA axis activation in patients with IBS.

Response of HF amplitude (which corresponds to para sympathetic activity) to both stimuli were not significantly different, however, recovery from psychological stimulus (which requires cognitive function), but not from physical stimulus, in GI subjects was significantly less and slower than controls. Responses to various types of stressors are supposed to initiate in prefrontal area, be processed and evaluated of its biological meaning, and the information of the evaluated meaning is transferred to peripheral autonomic branches via hypothalamus, and autonomic responses to the stress are observed. The Stroop test would induce processing and evaluation of its biological meaning in prefrontal cortex, whereas the cold pressor test would not require such process since this test is quite simple, and the information would probably be transmitted almost directly to hypothalamus and to peripheral autonomic branches. This possibly means autonomic response characteristic itself is not so different between GI group and control group. On the contrary, the difference in recovery phase from the Stroop test may mean the difference in cognitive function related process between both groups. The cognitive function related process would possibly involved in central emotional processing system. This may indicate that the delayed recovery from a psychological stimulus may be due to altered emotional processing in GI subjects other than altered autonomic response style, since recovery from physical stimulus was not significantly different from healthy controls. Elsenbruch et al., described enhanced negative emotional responses to stressful events in patients with IBS, despite their normal appraisal of the stressor [4]. Recovery from various psychological stimuli may be delayed due to altered central emotional processing and the effects of the stimuli may be sustained in brain networks associated with emotion modulation in patients with IBS. There were some reports about structural and neurophysiological brain changes associated with IBS, and the authors suggested the possibility that these brain changes may be a primary cause of IBS [14,48-50]. The prolonged effects of stressor may result in sustained increase

of HPA axis activity which would modulate gastric emptying and colonic motility [15-17], and may consequently induce various abdominal symptoms as well as anxiety. That is, stress reduction system in the brain may be fragile in patients with IBS, and this fragile stress reduction system could play a major role in the pathophysiology of IBS.

Mezzacappa et al., indicated that alterations in the baroreflex sensitivity was associated with vagal rebound after psychological stress [51]. The lowered baroreflex sensitivity in GI subjects may have some correlation to the attenuated recovery of HF amplitude from the Stroop test in this study.

Any autonomic indices were not significantly correlated with pre-stimulus basal score of T-A subscale in POMS. Myers and Greenwood-Van Meerveld reported the uncoupling of the effects of corticosterone (one of the members in HPA axis) on anxiety and colonic hypersensitivity [52]. The fact that there was no correlation between autonomic indices and basal tension-anxiety level may suggest differential effects of stressors to emotional pathway and to autonomic nervous system.

The result of the study should be cautiously interpreted, because of the following reasons. First, any laboratory or endoscopic examinations were not administered to potential candidates to minimize the loads on them, and subjects were selected only by the questionnaire based on Rome III criteria. Therefore, subjects with inflammatory bowel disease or the other organic bowel disease might have been included in the study, though the prevalence of organic bowel diseases is much lower than IBS.

Secondly, the results should have been analyzed in relation to the subtypes of IBS, but all subtypes were analyzed together since the sample size was small. There may be some differences in response style to stressful stimuli across subtypes of IBS.

Conclusions

Higher basal tension-anxiety, lower baroreflex sensitivity, and less and delayed HF amplitude recovery from the Stroop test, but not from the cold pressor test, were found in females with GI symptoms (who met Rome III criteria for IBS). This possibly means that autonomic response characteristic itself is not so different, but cognitive function related process would be different between GI group and control group, since the Stroop test would require higher cognitive processing and evaluation of its biological meaning, whereas the cold pressor test would not require such process. Then, it is plausible to hypothesize that autonomic and/or mood recovery from a psychological stimulus may be delayed due to altered central emotional processing, and the prolonged effects of the stimulus could accumulate and consequently contribute to various abdominal symptoms and anxiety in females with IBS.

Competing interests

The author declares that he has no competing interests.

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