Abstract This study examined the specific physiological responses of women with primary dysmenorrhea during the severely painful menstrual (days 1–2 of menstruation) and the non-painful follicular phases (days 5–8 after the onset of menstruation). Subjects consisted of 10 severe primary dysmenorrheic (Group P) and 10 non-dysmenorrheic women (Group C) with regular menstrual cycles. However, only 9 out of 10 and 8 out of 10 subjects of Groups P and C participated during the follicular phase. Physiological measures were taken in a resting state for 60 min. In the menstrual phase, the pain ratings and secretory immunoglobulin A (s-IgA) concentrations of Group P were significantly higher than those of Group C, with relatively significant decreases in the leg-skin temperature in the former as well. In addition, the systolic (SBP) and diastolic blood pressure (DBP) at 45 min after rest in Group P were significantly higher than those found in Group C. These reactions strongly suggest activation of the sympathetic-adrenal–medullary axis (SAM axis) by painful stress. Furthermore, the low-frequency (LF) component of the SBP variability (SBPV) was significantly higher in Group P than Group C, even during the follicular phase. These findings imply that Group P may well have elevated activities of the SAM axis throughout the whole menstrual cycle. As such, it suggests that dysmenorrheic women may be affected by certain stressors other than pain per se and pain-derived emotions throughout the whole menstrual cycle. The findings also indicate that women with dysmenorrhea have more sensitive responses to the SAM system than non-dysmenorrheic women during stress. Moreover, the high-frequency (HF) component of heart rate variability (HRV), or the index for the vagus nerve activity, displayed a consistently higher value in Group P than C. It is postulated that the human body may have responded to pain in an attempt to maintain the homeostatic state by enhancing vagus nerve activity. J Physiol Anthropol Appl Human Sci 24(6): 601–609, 2005 http://www.jstage.jst.go.jp/browse/jpa [DOI: 10.2114/jpa.24.601]

Keywords: dysmenorrhea, pain, autonomic nervous activity, secretory immunoglobulin A, sympathetic-adrenal-medullary axis

Introduction

Primary dysmenorrhea is a common gynecological complaint among young women. Symptoms of primary dysmenorrhea include spasmodic pains that usually occur just before or at the onset of menstruation, and are usually felt in the lower abdomen, with noxious effects occasionally radiating to the back and thighs. Primary dysmenorrhea, a condition associated with ovulatory cycles, is due to myometrial contractions induced by prostaglandins originating in secretory endometrium, which results in uterine ischemia and pain. Previous studies have demonstrated that primary dysmenorrhea affects more than 70% of young women (Andersch and Milsom, 1982; Teperi and Rimpela, 1989; Jamieson and Steege, 1996; Hillen et al., 1999; Balbi et al., 2000), and results in absenteeism and economic loss (Dawood, 1993). According to results of a study on the differences in pain perception of dysmenorrheic and non-dysmenorrheic women by Granot et al. (2001), latencies of laser-stimulated pain-evoked potentials were significantly longer throughout the menstrual cycle in the former. Hapidou and Catanzaro (1988) and Giamberardino et al. (1997) found a difference in the pain sensitivity between dysmenorrheic and non-dysmenorrheic women. In other studies on dysmenorrhea, pains have been relieved with various treatment approaches that include non-steroidal anti-inflammatory drugs (Namavar Jahromi et al., 2003; Mehlisch et al., 2003; Milsom et al., 2002), oral contraception (Milsom and Andersch, 1984; Davis and Westhoff, 2001; Callejo et al., 2003), acupuncture (Helms, 1987; Habek et al., 2003), transcutaneous electrical nerve stimulation (Dawood and Ramos, 1990; Kaplan et al., 1997), and microwave diathermy treatment (Vance et al., 1996). However, results of these treatments were subjective. It is now well established that the central nervous system (CNS), autonomic nervous system
(ANS), the endocrine system, and the immune system interact with each other (Glaser and Kiecolt-Glaser, 1998), but questions of multiple systems related with physiological responses in dysmenorrheic women have yet to be investigated.

Dmitrovic (2000) found that women with primary dysmenorrhea have elevated Doppler indices in uterine arteries not only on the first day of the cycle but throughout the whole cycle, suggesting impaired blood flow. In fact, it is not only a disorder of menstruation but also a disease of the menstrual cycle as a whole. The results imply that specific physiological responses of dysmenorrheic women are not only disorders induced by menstrual pain. As such, it is possible that disorders continue to affect dysmenorrheic women during the menstrual cycle, even during a state where the subject experienced attenuated psychological pain or were without any pain at all during the period. In other words, dysmenorrheic-specific physiological responses in affected women may manifest obvious signs compared to non-dysmenorrheic women during the severely painful menstrual and the non-painful follicular phases. Therefore, we can obtain useful information from dysmenorrheic-specific physiological responses as useful information to adopt a certain strategy in suppressing and minimizing the noxious physiological load induced during the menstrual cycle. And those results may lead to a reduction of economic loss from absenteeism due to incapacitating dysmenorrhea, as well as yielding meaningful information on physiological anthropology one of the goals of which is improvement in the quality of human life by investigation of the physiological capabilities of the human body. Also, the information is useful in terms of physiological polymorphisms and whole body coordination which are important concepts of physiological anthropology (Maeda, 2005; Kouda, 2005; Yasukouchi, 2005; Sato, 2005).

Dysmenorrheic women are one of various physiological types among humans. By comparing the physiological differences between dysmenorrheic and non-dysmenorrheic women, the underlying processes which generate physiological polymorphisms may be identified. In particular, we can observe whether dysmenorrheic women could maintain homeostasis within the human body by physiological mechanisms in response to dysmenorrhea-induced pains during the menstrual phase. In other words, we can elucidate their physiological responses from their whole body coordination. The present study endeavored to evaluate certain dysmenorrheic-specific physiological indexes in affected women and compared them with those of non-dysmenorrheic women during the menstrual and follicular phases.

Methods

Subjects

The subjects consisted of 10 severe primary dysmenorrheic (Group P) and 10 non-dysmenorrheic women (Group C) with regular menstrual cycles. Group C was comprised of women who reported no pain during menstruation. Groups P and C did not differ in age (23.6±4.2 vs. 21.8±1.9 years, respectively), height (159.3±4.1 vs. 160.1±4.3 cm, respectively), and weight (55.18±6.8 vs. 52.95±4.0 kg, respectively). All subjects were in good health, not taking any prescription medication including oral contraceptives or psychotropic agents, and of normotensive BP status. Subjects were instructed to refrain from using any analgesic drug for 24 hr prior to testing, and from eating, drinking, smoking, and exercising for at least two hours before the experiment. Written informed consent was obtained from all subjects after a full explanation of the experimental purpose and protocol. The subjects in the experiment put on similar attire such as briefs, short pants and T-shirts, without brassieres.

Experimental design

Experiments were conducted in a climatic chamber maintained at 27°C with a relative humidity of 50%. The women were examined twice throughout the menstrual cycle: days 1–2 of menstruation (the most painful period; Experiment I), and the non-painful period during the follicular phase (days 5–8 after the onset of menstruation; Experiment II). Note that only 9 out of 10 and 8 out of 10 subjects of Groups P and C participated in Experiment II, respectively. Experiment II was conducted in a different menstrual cycle after Experiment I. Dysmenorrheic and non-dysmenorrheic women were investigated in Experiment I, and pain during the menstrual phase was elucidated; viz., pain per se and specific physiological responses induced by pain-related emotion.

In Experiment II, the physiological responses during the non-painful follicular phase of the two similar groups compared dysmenorrheic and non-dysmenorrheic women. If specific responses in pain per se and pain-derived emotion-induced physiological responses could be discriminated in dysmenorrheic women in the menstrual phase, different physiological responses were indicated in the non-painful follicular phase. However, if the specific physiological responses of dysmenorrheic women were similarly induced in the follicular phase, it is possible that factors other than pain per se and pain-derived emotions were involved in the follicular phase. Experiments I and II shows similarities and differences between the two groups.

Measurements of physiological indexes

We measured physiological responses such as electrocardiography (ECG), blood pressure (BP: diastolic blood pressure or DBP, and systolic blood pressure or SBP), the low-frequency component of systolic blood pressure variability (LF component of SBPV), secretory immunoglobulin A (s-IgA) and cortisol in saliva and pain ratings. Skin temperature was measured by thermistors placed on the forehead, chest, forearm, hand, thigh, leg and foot. The lower abdominal temperature was measured at the following three points: points LAT1 (lower abdominal temperature-1) and LAT2 at 1 and 5 cm posterior to the umbilicus along the mid line respectively, while LAT3 was taken at point 10 cm left
and 3 cm posterior to the umbilicus. Skin temperature and LAT were recorded in a portable data logger (LT-8A, Gram, JAPAN).

ECG measurement (PC-386GE, EPSON; Multichannel Amplifier MEG-6100, JAPAN) was performed by synchronizing respiratory systemic control at 0.25-Hz metronorm for 180 sec. From the ECG monitoring, heart rate (HR) and heart rate variability (HRV) were derived. Many studies have reported the reliability of HRV as a noninvasive index of ANS activity (Ishibashi et al., 1999; Miyatsuji et al., 2002). The high frequencies (HF) of HRV relate to parasympathetic activity, while the low frequencies (LF) of HRV are associated with both parasympathetic and sympathetic activities (Pomeranz et al., 1985). And the LF/HF ratio of HRV was proposed as an index of sympatho-vagal balance by Pagani et al. (1986). The high frequencies (HF) of HRV relate to parasympathetic activity, while the low frequencies (LF) of HRV are associated with both parasympathetic and sympathetic activities (Pomeranz et al., 1985). And the LF/HF ratio of HRV was proposed as an index of sympatho-vagal balance by Pagani et al. (1986). In addition the LF component of SBPV, which has been reported to relate closely to the SNS-balance by Pagani et al. (1986). In addition the LF component of SBPV, which has been reported to relate closely to the SNS-balance by Pagani et al. (1986). The heart period sequences, obtained by detecting the peak of the R wave in an ECG, were converted into beats/min and interpolated into 10 Hz equidistant data. Spectral analysis of HRV was applied to the time series data of R-R intervals for every 3 min, by Fast Fourier Transformation (FFT) using a Hamming window. The LF and HF components were integrated from 0.05 to 0.15 Hz and 0.15 to 0.40 Hz of the power spectra, respectively.

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Data analysis

The ECG data were digitized with a sampling frequency of 1 KHz on a personal computer equipped with a 12-bit analog-to-digital converter (MICROSCIENCE ADM-5298BPC, JAPAN). The heart period sequences, obtained by detecting the peak of the R wave in an ECG, were converted into beats/min and interpolated into 10 Hz equidistant data. Spectral analysis of HRV was applied to the time series data of R-R intervals for every 3 min, by Fast Fourier Transformation (FFT) using a Hamming window. The LF and HF components were integrated from 0.05 to 0.15 Hz and 0.15 to 0.40 Hz of the power spectra, respectively.

We continuously monitored BP using the Finapres (Ohmeda, 2300Finapres, USA) with a digit cuff applied around the left middle finger and the hand supported comfortably by the subject’s side, at heart level. This noninvasive BP monitor uses the vascular unloading technique to determine systolic, diastolic BP on a beat-by-beat basis.

Measurements derived from skin temperature and LAT were continuously recorded, and the mean values of these measurements were derived at 5-min intervals.

s-IgA and cortisol in saliva measurements

In investigating the s-IgA and cortisol levels in saliva, we collected samples using 2 pieces of Salivette (Sarstedt Ltd., Germany) at the sublingual site for 5 min. After collection, saliva was extracted from the cotton by centrifugation (KUBOTA 2700, JAPAN) at 3.5×10^3 rpm for 15 min before storage at −30°C.

The concentration of s-IgA in saliva was determined by enzyme-linked immunosorbent assay (ELISA). Saliva aliquots (20 µl) were assayed at a dilution of 1:1,000. The coating antibody was antihuman secretory component (2 µg/ml) at 100 µl per well. After incubation for 2 h at 37°C, wells were washed with wash buffer (Nacl 16 g, KCl 0.4 g, Na2HPO4 2.3 g, KH2PO4 0.4 g, Tween 200 ml, 1999 ml of deionized water). Assays were performed in triplicate against a range, 0–1,000 ng/ml, of standard Human IgA. A reference sample was incorporated into each plate. After incubation for 2 h at 37°C, wells were washed with wash buffer. For detection, an HRP-conjugated goat antihuman IgA (1:2,000) was used, directed against human IgA heavy chain. Incubation wells were filled with substrate solution (0.2 M Na2HPO4 soln, 0.1 M citric acid, ABTS, 30% H2O2) and incubated for 30 min. The reaction was stopped with NaF soln (1.25%). Developed color was measured in a Microplate Reader (BIO-RAD Model 550, JAPAN). Each 5-min sample provided a measure of the saliva s-IgA concentration (µg/ml) and saliva volume (ml/min). The

Procedures

Dysmenorrheic and non-dysmenorrheic subjects sat on a chair in a resting state for 60 min in both Experiments I and II. In addition to this 60-min resting state, seated subjects were allowed a further 20-min resting state after electrode placements. Measurements of physiological indexes that included ECG, BP and pain ratings were taken at 15-min intervals while saliva was sampled at 30-min intervals. Furthermore, skin temperature and LAT were continuously recorded at 30-sec intervals. In Experiment II, procedures of electrode placement and the various physiological indexes in Experiment I were repeated with similar paradigm and time intervals. Note that pain ratings, skin temperature and LAT were not monitored in the subjects during the follicular phase as pain was not physiologically induced during this phase.

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s-IgA secretion rate (µg/min) was calculated from the formula 
secretion rate = concentration × volume.

Levels of cortisol were determined by using a Cortisol ELISA Kit (Oxford Biomedical Research, Inc. USA). Cortisol standards were prepared by diluting a stock solution of cortisol (1 µl/ml). Fifty microliter of standards or saliva was added to the appropriate wells in the anticortisol rabbit antibody precoated microplate. To each well, 50 µl of the diluted cortisol enzyme conjugate was also added. The plate was then incubated for 1 h at room temperature and then washed three times with buffer in an automatic microtiterplate washer (AMW-2 ASAHI TECHNOGLASS, Inc., JAPAN). 150 µl of substrate (stabilized 3,3', 5,5' Tetramethylbenzidine (TMB) plus Hydrogen Peroxide (H₂O₂) in a single bottle) was added to the wells. The plate was then incubated at room temperature for 30 min to allow the color to develop; this reaction was stopped by the addition of 50 µl of 1 N HCl. Each plate was read at 450 nm with a Microplate Reader (BIO-RAD Model 550, JAPAN). The cortisol concentrations were determined from a standard curve.

**Statistical analysis**

All data was expressed as mean±standard errors (SE). All parameters were analyzed by two-way ANOVA with repeated measures. Variance analyses (ANOVA tests) were separately performed in the menstrual and follicular phases. The factors were group and period. Post-hoc comparisons of the mean values were done by using the Tukey HSD. Statistical analyses were performed on a personal computer using software SPSS 11.5J (SPSS Japan Inc.), and differences with a probability value of less than 0.05 were considered significant.

**Results**

**Experiment I (menstrual phase)**

Results of ANOVA revealed that the following exhibited the main effects of group: lower abdominal pain (F(1, 18)=63.32), lower back pain (F(1, 18)=31.69), while pain ratings indicated significantly higher values in Group P than Group C (Fig. 1).

In one subject of Group C, the yield of saliva volume required for analysis was inadequate, and she was thus excluded from Experiment I analysis. Significant effects of period emerged for both the saliva volume (F(1, 17)=4.67; p<0.05) and secretion rate of s-IgA (F(1, 17)=11.20; p<0.01). Post-hoc multiple comparisons showed that both the saliva volume (p<0.05) and secretion rate of s-IgA (p<0.01) significantly decreased at 60 min compared with 30 min after sampling. With regard to s-IgA concentrations, a significant main effect of group was obtained, (F(1, 17)=4.85; p<0.05). The s-IgA concentration was significantly (p<0.05) higher in Group P than Group C (Fig. 2). No significant effects emerged for cortisol concentration.

**Fig. 1** Scores of lower abdominal and back pains in primary dysmenorrheic (Group P, N=10) and non-dysmenorrheic women (Group C, N=10) during the menstrual phase. Values are mean±SE. *p<0.05.

Based on ANOVA analyses of HRV indexes, a significant main effect of group was observed for the HF component of HRV, (F(1, 18)=5.77; p<0.05). Group P had a significantly (p<0.05) higher HF component of HRV relative to Group C at 30, 45 and 60 min (Fig. 3). However, significant effects were not established in HR, LF component or LF/HF ratio of HRV. Interestingly, significant group×period interactions were derived in SBP (F(3, 54)=3.46; p<0.05, Fig. 4A) and DBP (F(3, 54)=2.78; p<0.05, Fig. 4B). The BP at 45 min during resting indicated more significant (p<0.05) increases in Group P than Group C. No significant effects were derived from the LF component of SBPV.

**Fig. 2** Concentration of secretory immunoglobulin A (s-IgA) in primary dysmenorrheic (Group P, N=10) and non-dysmenorrheic women (Group C, N=9) during the menstrual phase. Values are mean±SE. *p<0.05.

From ANOVA-tested results in skin temperature, a significant group×period interaction was indicated in the leg-skin temperature (F(13, 234)=2.20; p<0.01, Fig. 5). Leg-skin temperatures exhibited significantly (p<0.05) lower values 0, 5, 10, 15 and 35 min after testing in Group P than C (Fig. 5). Moreover, significant effects of period were obtained in the forehead (F(13, 234)=2.19; p<0.05), forearm (F(13, 234)=30.14; p<0.01), hand (F(13, 234)=21.05; p<0.01), foot (F(13, 234)=3.75; p<0.01) and chest skin temperatures.
Except for the chest skin temperature, all indexes indicated significantly decreasing tendencies with time. Significant effects of group emerged for both LAT1 (F(1, 18)=7.79; p<0.05) and LAT3 (F(1, 18)=6.23; p<0.05). Both LAT1 (35.34±0.3 vs. 34.02±0.3) and LAT3 (35.27±0.2 vs. 34.54±0.2) scored significantly higher values in Group P than C.

**Experiment II (follicular phase)**

No significant effects were derived in the saliva volume, secretion rate and concentration of s-IgA. As the yield of saliva volume required for cortisol analysis was inadequate, one subject in Group C was excluded from Experiment II analysis. A significant main effect of period was observed in the cortisol concentration (F(1, 14)=4.86; p<0.05), which indicated significant increase at 60 min compared with 30 min after sampling.

ANOVA analyses neither indicated significant main effects

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in factors of group and period nor detected significant group×period interactions in HR, LF and HF components or LF/HF ratio of HRV. A significant main effect of period (F(3, 45) = 15.37; p < 0.05) as well as a group×period interaction (F(3, 45) = 2.97; p < 0.05) emerged for SBP. As for DBP, a significant main effect of period was obtained (F(3, 45) = 16.8; p < 0.01), and both SBP and DBP showed significant time-related increases. A significant main effect of group was obtained in the LF component of SBPV (F(1, 15) = 4.66; p < 0.05), which indicated significantly (p < 0.05) higher values in Group P than Group C (Fig. 6).

**Discussion**

*High activities of the sympathetic-adrenal-medullary (SAM) axis in dysmenorrheic women during the menstrual and follicular phases*

The present study elucidated dysmenorrheic-specific physiological responses in affected women by comparing certain relevant physiological indexes during the menstrual and follicular phases in women with (Group P) and without (Group C) dysmenorrhea. Pain ratings (Fig. 1) of the lower abdominal and back regions as well as s-IgA concentration (Fig. 2) in Group P scored significant increases compared with Group C. According to Winzer et al. (1999), Ring et al. (1999) and Bosch et al. (2001), acute stress induced by mental arithmetic and memory test significantly enhanced concentration of s-IgA. As such, an increase in the s-IgA concentration in the present study implies that Group P was probably under the influence of pain stress.

Endogenous releases of algic substances such as bradykinins and algesia-potentiating prostaglandins induced by pain generally produce local heat (Yokota, 1997). Compared with Group C, the markedly high LAT in Group P was likely to have been influenced by the pain-induced focal pyretic action. There are two major physiological systems involved in stress response: the catecholamine-producing SAM system and the cortisol-releasing hypothalamic-pituitary-adrenal (HPA) axis. When stressors act on the SAM system, BP, HR and sweating rate are promoted besides inducing peripheral vasoconstriction. In the present study, stress responses were observed to have likely been induced via the SAM system when physiological indexes of dysmenorrheic (Group P) and non-dysmenorrheic (Group C) women were compared. The DBP and SBP values at 45 min during the resting period were significantly higher in Group P than C (Fig. 4A, 4B) in the menstrual phase. Muscle tension is increased and vasoconstriction is commonly induced when the human body experiences pain, and blood flow to the painful sites is reduced to yield ischemia (Yamamura and Kaneko, 1997). According to findings by De Marinis et al. (1995), BP and the HF component of HRV increased and heart rate decreased during the cluster headache. In short, the increase in BP observed in Group P may be caused by vasoconstriction induced by pain. Said vasoconstriction might have also affected the leg-skin temperature as cited temperature values in Group P were significantly attenuated compared with the controls (Fig. 5). While such SAM-derived physiological responses were not confined to the menstrual phase, similar responses were observed in the follicular phase as well; viz., the LF component of SBPV in the follicular phase maintained approximately higher readings in Group P than Group C (Fig. 6). The LF component of SBPV comprises mainly the vasomotor nerve, which reportedly associates closely with the α-sympathetic nervous system (Oka et al., 1992). As such, the vasomotor activity-regulating sympathetic nervous system (SNS) activity remains elevated to probably increase peripheral vascular resistance, even during the non-painful follicular phase in Group P (vs. Group C). In other words, the vaso-SNS activity of Group P is elevated not only in the menstrual phase, but persists to affect the follicular phase as well. In short, it is highly possible that the stress responses elicited via the SAM system in Group P continue to ripple throughout the whole menstrual cycle. Based on these findings, dysmenorrheic women may have to endure certain stressors other than pain sensations per se or pain-derived emotion-induced factors. Our results coincide well with findings observed by Dimitrovic (2000) in that uterine blood flow is attenuated (indicated by elevated Doppler indexes) throughout the menstrual cycle in women with primary dysmenorrhea; viz., disorders are not only experienced during the menstrual phase but also throughout the whole menstrual cycle.

Based on the present results, it is plausible that women with dysmenorrhea have more sensitive responses to the SAM system than non-dysmenorrheic women during stress. This implies that the level of sensitivity to the SAM axis may be associated with the presence of dysmenorrhea. In other words, it suggests that sensitivity to the SAM system may be cited as one of the factors which generate the physiological polymorphisms in the dysmenorrhea.
Activation of vagus nerve activity to suppress dysmenorrhea-induced pain

In principle, SNS and parasympathetic nervous system (PNS) function via an antagonistic mechanism. In times when subjects suffered from severe physiological pain in the present study, the vaso-SNS activity was supposed to have been promoted in Group P (Fig. 4A, 4B). Furthermore, the HF component of HRV, an index of PNS activity, increases (Fig. 3). Three possible mechanisms may have contributed to elevated PNS activity: (I) possible regional differentiations of sympathetic efferents; (II) possible elicitation of the baroreceptor reflex; and (III) possible activation of the vagus nerve system to eventually suppress pain.

In Mechanism I, vasoconstriction-induced pain elevates α-SNS activity, which leads to reduction of β-SNS activity, resulting in a higher cardio-PNS activity to produce a higher HF component of HRV. In this study, however, the time-related BP increased (Fig. 4A, 4B) without affecting the β-SNS activity. The effects were probably not confined within certain SNS regions, i.e., regional differentiations of sympathetic efferents. In Mechanism II, the cardioinhibitory center of the vagus nerve system is generally mimicked to antagonize an increase in BP, resulting in elevating the HF component of HRV. Interestingly, although increases are observed in the time-related BP elevations (Fig. 4A, 4B), the HF component of HRV continues to universally maintain a high value equivalent to those registered from the early stage of BP elevations (Fig. 3). The baroreceptor-reflex mechanism may therefore be inadequate to account for this phenomenal non-response in the HF component of HRV to time-related BP increases. In Mechanism III, Kirchner et al. (2000) have found that vagus nerve stimulation attenuates pain, while Thies and Foreman (1983) and Chandler et al. (1991) have reported that stimulation of cervical, thoracic and cardiac vagal afferents suppresses secondary nociceptive neuronal activities via the spinothalamic and spinoreticular tracts of the nociceptive ascending spinal pathways. These findings suggest that vagus nerve stimulation is associated with pain suppression. The human body espouses a homeostatic mechanism to maintain a physiological state of equilibrium by generally adjusting the endogenously multifaceted mechanisms to respond to external stimuli in the surrounding environment. In the present study, the uniformly maintained elevated values in response to dysmenorrhea-induced pain by the HF component of HRV in Group P was probably due to elicitation of the endogenous homeostasis within the human body to trigger relevant inhibitory mechanisms to cancel out externally mimicked disturbing stimuli so a stable condition was thus sustained.

From the above findings, it appears that stress responses via the SAM system emerge and probably ripple throughout the menstrual cycle in dysmenorrheic women. As such, affected women may experience certain stressors other than the dysmenorrhea-induced pain per se and/or the pain-derived emotional factors during the menstrual cycle. It seems quite likely that women with dysmenorrhea have more sensitive responses to the SAM system than non-dysmenorrheic women during stress. The relationship between the reaction to the SAM system and the presence of dysmenorrhea suggests that sensitivity to the SAM system may be cited as one of the factors which lead to the physiological polymorphisms in women of reproductive age. Furthermore, it is postulated that the human body attempts to maintain homeostasis within the system by elevating vagus nerve activity in order to attenuate or neutralize pain in dysmenorrheic-affected women during the menstrual cycle. Their findings may show an example of whole body coordination. In addition, it is necessary to further research the causal relationship between the level of sensitivity to the SAM axis and the presence of dysmenorrhea.

Acknowledgments This study was supported by the Grant-in-Aid for Scientific Research (grant no. 15107006) from the Japanese Ministry of Education, Culture, Sports, Science and Technology, and in part by Grant-in-Aid for the 21st Century COE Program.

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Received: April 4, 2005
Accepted: September 26, 2005
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