Relationship between Sympathoadrenal and Hypothalamicpituitary- adrenal Response during Colorectal Distention in Patients with Irritable Bowel Syndrome and Healthy Controls

VII. 7. Relationship between Sympathoadrenal and Hypothalamic-pituitary-adrenal Response during Colorectal Distention in Patients with Irritable Bowel Syndrome and Healthy Controls

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Corticotropin-releasing hormone (CRH) mediates stress responses in the brain-gut axis. Administration of CRH modulates brain activation and the autonomic nervous system in response to colorectal distention. Increased hypothalamic-pituitary-adrenal (HPA) responses to stress stimulation alter the balance between afferent and efferent neural pathways. We have found that activity in brain regions implicated in CRH secretion, such as amygdala and hippocampus, are suppressed during visceral stimulation in men with IBS[1)]. The noradrenaline system hub is found in the locus coeruleus (LC), which sends neural projections to the amygdala and hypothalamus, which in turn contain numerous CRH receptors. The LC also sends major projections to the frontal cortex, which is able to regulate the amygdala[2)]. Male IBS patients likely exhibit a similar pattern both in the amygdala and in plasma noradrenaline levels following CRH injection during stimulation[1] in our previous report. These findings implicate parallel modifications in the HPA and catecholamine pathways. The catalytic activity of phenylethanolamine N-methyltransferase (PNMT), which is the enzyme that synthesizes adrenaline from noradrenaline, is regulated by cortisol, and stress induces adrenal PNMT activity[3)]. Nociceptive stressors induce a strong correlation between ACTH levels and catecholamine levels[4)]. Nevertheless, how the HPA-catecholamine network is modulated during visceral stress in IBS patients remains unknown. Sex differences in central nervous system responses to visceral stress, perception, and motility have also been reported in patients with IBS. Here, we hypothesized the relationship between sympathoadrenal and hypothalamic-pituitary-adrenal (HPA) responses to colorectal

distention in patients with irritable bowel syndrome (IBS).

We enrolled 32 patients with IBS (16 women and 16 men) and 32 healthy subjects (16 women and 16 men), and randomly divided them between CRH and saline injection groups. All of the patients with IBS were diagnosed based on the Rome lll criteria[5]. The State-Trait Anxiety Inventory and Self-Rating Depression Scale were used to assess their anxiety and depression levels and showed no significant differences between IBS and HC groups. This study was approved by the Ethics Committee of the Tohoku University Graduate School of Medicine, Japan. We used the barostat protocol. A bag was inserted into the colorectum. The catheter was then connected to computerized barostat equipment (Synectics Visceral Stimulator; Medtronics Synectics; Shoreview, MN). The patients randomly underwent no (0 mmHg), mild (20 mmHg), or strong (40 mmHg) colorectal distension. CRH (2 μg/kg) or saline was then administered via injection, and the distention protocol was repeated. Blood samples were obtained from an intravenous cannula after each period, and subjective symptoms were evaluated using an ordinate scale[1]. The heart rate (HR) and HR variability (HRV; calculated as the low [LF, 0.04–0.15 Hz] to high frequency [HF, 0.15–0.4 Hz] peak ratio, LF/HF) were analyzed using electrocardiography (SCM 6000; Fukuda Denshi; Tokyo, Japan). R-R intervals during the distention were calculated using computer software (R-R Interval Analyzing Program, HPS-RRA; Fukuda Denshi). Plasma noradrenaline, adrenaline, adrenocorticotropic hormone (ACTH), and cortisol levels were measured at the time of each distention. Data were analyzed using SPSS 21.0 (IBM Corporation; Armonk, NY, USA). An overall generalized estimating equation (GEE) analysis (SPSS 21.0, IBM Corp.) was performed during the random distention. Network analyses within the neuroendocrine system were conducted using structural equation modeling in Amos 22.0 (IBM Corp.). A satisfactory model usually has a comparative fit index ≥ 0.95 and a root mean square error of approximation < 0.05.

We found sex-based differences in plasma noradrenaline levels, but not in plasma ACTH, serum cortisol, or plasma adrenaline. As a result, the following analyses were performed on data from each subgroup in the IBS and HC groups, including both men and women. In HCs receiving a placebo injection, plasma ACTH and noradrenaline levels were negatively correlated (rho = –.609, P = .012) during 40 mmHg distention, but were unrelated to plasma adrenaline levels. ACTH levels in IBS patients receiving a placebo injection were positively correlated with cortisol levels (40 mmHg distention: rho = .818, P < .001). ACTH levels were also significantly correlated with adrenaline levels during 40 mmHg distention

(rho = .605, P = .013). ACTH and plasma adrenaline levels were not significantly correlated in these participants in the 40mmHg distention condition.

Structural equation modeling was used to analyze the relationship between ACTH-cortisol and noradrenaline-adrenaline, assess network differences between IBS and HC groups, and examine the effect of CRH on these relationships. (Figure 1) The model fit was tested together for the CRH and saline groups in both the IBS and HC groups (χ 2(4) = 1.706, P = .790, comparative fix index = 1.000, root mean square error of approximation = .000, 95% CI = 0.000–0.126). Higher plasma ACTH levels in patients with IBS were associated with higher levels of serum cortisol (β = .94, P < .001); we found a similar association with plasma adrenaline levels (β = .972, P < .001) during 40mmHg distention in IBS patients were administered saline, and plasma ACTH levels in IBS patients who were administered CRH (cortisol: β = .711, P < .001; adrenaline: β = .496, P < .001). In contrast, in HCs, plasma ACTH levels were significantly associated with serum cortisol levels in the placebo group (β = .744, P < .001).

GEE analysis showed a significant distention × group × drug interaction (P = .016) for HF power, but not HR or LF/HF ratio (HR, P = .939; LF/HF ratio, P = .408). There were no significant distention × group × drug × sex interactions with any of the HRV parameters (HR, P = .295; HF, P = .197; LF/HF ratio, P = .110). Spearman's correlation analysis showed significant correlations between plasma adrenaline levels and HR, as well as HF power, for all levels of distention, in HCs who were administered CRH. (Table 1) In addition, there was a significant correlation between the LF/HF ratio and plasma adrenaline levels in these participants during the 40mmHg distention. The plasma adrenaline levels and HRV were not correlated in patients with IBS, but there was a significant correlation between HR and plasma ACTH levels, as well as serum cortisol levels, during the 40mmHg distention in the IBS placebo group.

The relationship between HPA-sympathoadrenal responses and CRH levels during colorectal distention differs between IBS patients and controls. The threshold for ACTH-induced adrenaline release was enhanced only during strong distention in HCs. In contrast, there was a correlation in the IBS group, even in the absence of distention. We have provided evidence for sex-based differences in plasma noradrenaline levels, but not in plasma ACTH, serum cortisol, or plasma adrenaline levels. Interpretation of the results herein must therefore account for the influence of the mensuration cycle in women. In conclusion, modulation of

adrenal gland activity in response to ACTH stimulation may contribute to the brain-gut pathophysiology characteristic of IBS.[6)]

References

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Table 1. Features of HRV during 40 mmHg distention and correlation between HRV and neuroendocrine variables. Data are shown as rho scores of the Spearman rank correlation coefficient. Data for %HF or LF/HF were used to assess the correlations with plasma ACTH, serum cortisol, plasma adrenaline, and noradrenaline levels. *P < 0.05, **P < 0.01. HR, heart rate; HF, high frequency; LF, low frequency; Ad, adrenaline; NA, noradrenaline; ACTH, adrenocorticotropic hormone; SD, standard deviation.

Variable	Mean	SD	ACTH	Cortisol	Ad	NA
HC with placebo injection (n = 16)						
HR	77.23	9.89	0.04	-0.28	0.45	-0.12
HF power	437.89	338.40	-0.11	0.21	-0.39	-0.04
LF/HF	2.48	1.55	-0.37	-0.02	-0.31	0.42
HC with CRH injection (n = 16)						
HR	83.73	19.08	0.25	0.44	0.77 **	0.37
HF power	658.02	993.43	-0.41	-0.51 *	-0.72 **	-0.29
LF/HF	4.38	2.92	0.10	0.20	0.66 **	0.38
IBS with placebo injection (n = 16)						
HR	73.48	12.30	0.58 *	0.54 *	0.22	0.17
HF power	931.64	1725.64	-0.22	-0.05	0.10	-0.28
LF/HF	3.18	2.79	-0.13	-0.38	-0.24	0.25
IBS with CRH injection (n = 16)						
HR	80.27	11.96	0.21	0.21	0.44	-0.12
HF power	197.78	167.70	0.18	-0.07	-0.27	0.04
LF/HF	4.70	2.59	0.04	0.28	0.41	0.01

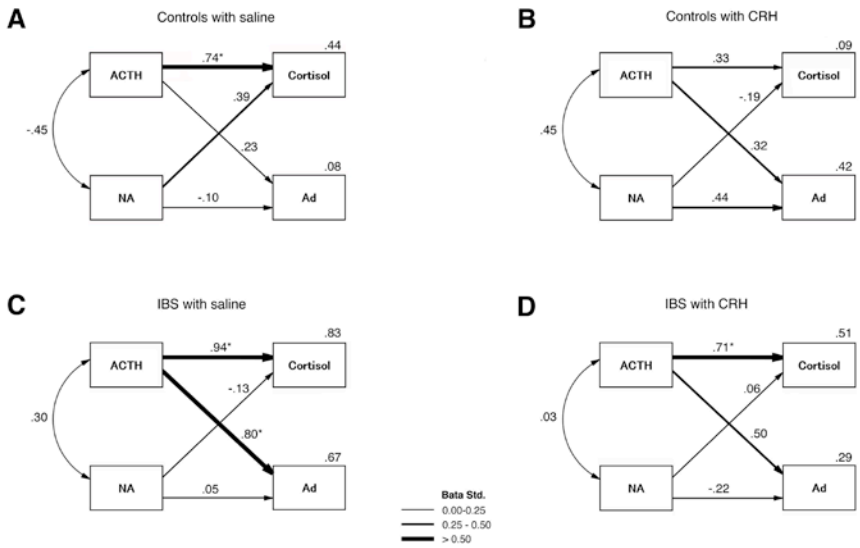

Figure 1. Neuroendocrine response models during 40 mmHg distention (A) HCs injected with saline (n= 16), (B) HCs injected with CRH (n = 16), (C) patients with IBS injected with saline (n = 16), and (D) patients with IBS injected with CRH (n = 16). *P < .0125 indicate significant paths. The squared multiple correlations (R2) of the variables are reported in the top right corner. There were no significant factor correlations between ACTH and NA. ACTH, plasma ACTH; cortisol, serum cortisol; HCs, healthy controls; NA, plasma noradrenaline; Ad, plasma adrenaline; ACTH, adrenocorticotropic hormone; IBS, irritable bowel syndrome; CRH, corticotropin-releasing hormone.