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Duodenal VIP and IL-1β Upregulation Associated with Sleep Disturbance in Functional Dyspepsia: A Cross-Sectional Study

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Abstract

Objective: To measure the expression levels of vasoactive intestinal peptide (VIP) and interleukin-1β (IL-1β) in the duodenal bulb mucosa of patients with functional dyspepsia (FD) and to analyze their relationship with sleep disturbance. **Methods:** Sixty patients with functional dyspepsia (FD) who attended Wuhan Puren Hospital between May 2024 and May 2025 were enrolled as the FD group; thirty healthy individuals undergoing routine physical examinations during the same period served as the control group. Both the FD and control subjects underwent painless gastroscopy. Immunohistochemistry was employed to quantify the expression of vasoactive intestinal peptide (VIP) and interleukin-1β (IL-1β) in the mucosa of the duodenal bulb. Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI). **Results:** Expression levels of VIP and IL-1β in the duodenal bulb mucosa were significantly higher in the FD group than in the control group ($p < 0.05$). No significant differences were observed among FD subtypes ($p > 0.05$). The PSQI score was markedly higher in the FD group than in controls ($p < 0.01$). FD patients with comorbid sleep disturbance exhibited higher duodenal VIP and IL-1β expression than FD patients without sleep disturbance ($p < 0.01$). Moreover, VIP and IL-1β expression levels were positively correlated with PSQI scores in the FD cohort ($p < 0.01$). **Conclusion:** VIP and IL-1β are aberrantly up-regulated in the duodenal bulb mucosa of FD patients, who also display impaired sleep quality. The deterioration of sleep in FD appears to be closely associated with elevated mucosal VIP and IL-1β expression within the duodenal bulb.

Keywords

Functional Dyspepsia, Duodenal Micro-Inflammation, VIP, IL-1β, Sleep Disturbance

1. Introduction

Functional dyspepsia (FD) is a common gastrointestinal disorder characterized by one or a group of upper-abdominal symptoms, including postprandial fullness, early satiation, epigastric pain, and epigastric burning [1]. The prevalence of FD is estimated at 10% - 40% in Western countries and 5% - 30% in Asia [2]. Currently, FD is classified into two subtypes: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS); however, its pathophysiology remains incompletely understood; previous studies suggest that visceral hypersensitivity and delayed gastric emptying are major contributors [3]. Recent studies have indicated that the duodenum may be a key site in the pathophysiology of FD [4], with mechanisms involving low-grade duodenal inflammation—characterized by mild increases in eosinophil and mast cell infiltration, elevated pro-inflammatory cytokines, and subtle epithelial barrier dysfunction without overt mucosal damage [5]. However, the specific molecular signaling pathways linking duodenal micro-inflammation to FD symptoms remain unclear. Vasoactive intestinal peptide (VIP) is a 28-amino-acid basic peptide that is widely distributed in the central nervous system, gastrointestinal tract, and endocrine organs, exerting multiple biological effects [6]. Interleukin-1β (IL-1β), a key member of the IL-1 family, participates in inflammatory and innate immune responses and is implicated in the pathophysiology of various diseases [7]. Comorbid sleep disturbance is common in FD, and FD patients with sleep disturbance usually have poorer quality of life [8]. Existing studies have shown a close association between sleep disturbance and intestinal inflammation [9]. The roles of VIP and IL-1β in FD and in the FD-sleep disturbance comorbidity remain unclear. Therefore, this study aims to measure the differences in VIP and IL-1β expression in the duodenal bulb mucosa between FD patients and controls, and to analyze their correlation with sleep disturbance, so as to provide evidence for the pathogenesis of FD and for research into the FD-sleep disturbance.

2. Clinical Data and Methods

2.1. Case Selection

From May 2024 to May 2025, 60 FD patients who fulfilled the Rome IV criteria were recruited at Wuhan Puren Hospital among out-patients and in-patients undergoing gastroscopy (24 PDS, 26 EPS, 10 overlap); 30 healthy subjects receiving routine physical examinations in the same period were enrolled as controls. The sample size was extrapolated from Komori *et al.* [10], who compared duodenal mucosal inflammatory markers between 24 FD patients and 14 controls, and was doubled to enhance statistical power and permit subgroup analyses. The study was approved by the Ethics Committee of Wuhan Puren Hospital (Approval No. 2024-016), and written informed consent was obtained from every participant.

2.1.1. Inclusion Criteria

1) Meeting the Rome IV diagnostic criteria [11] for FD and its subtypes;

2) Aged 18 - 75 years;

3) Endoscopy shows no obvious abnormality or only chronic superficial gastritis.

2.1.2. Exclusion Criteria

1) Organic diseases such as peptic ulcer, gastrointestinal tumor, reflux esophagitis, etc.;

2) Severe diseases of the heart, liver, kidney, lung, or other vital organs;

3) Pregnant or lactating women;

4) Incomplete clinical data.

2.2. Study Methods

2.2.1. Immunohistochemical Detection of VIP and IL-1β Expression

Functional dyspepsia is associated with increased immune-cell infiltration and altered mucosal permeability in the duodenal bulb; this region is therefore a relevant and sensitive site for investigating local inflammatory mediators such as VIP and IL-1β. All participants underwent painless gastroscopy, and one biopsy was taken from the anterior wall of the duodenal bulb. Biopsy specimens were fixed in 4% paraformaldehyde for 24 h, routinely paraffin-embedded, and cut into 4-μm serial sections. The EnVision two-step procedure was used: 3% H_2O_2 for 10 min to block endogenous peroxidase; citrate buffer antigen retrieval; incubation with rabbit anti-human VIP and IL-1β overnight at 4˚C; HRP-labeled secondary antibody for 30 min at 37˚C; DAB development, haematoxylin counterstaining, and neutral balsam mounting. Negative controls were performed by replacing the primary antibody with PBS.

2.2.2. Evaluation of Staining

Under 200× magnification with an OLYMPUS BX53 microscope, five random fields were selected; Image-Pro Plus 6.0 was used to measure the integral optical density (IOD) and area of positive staining, and the mean IOD/area was calculated as the relative expression level.

2.2.3. Sleep Quality Assessment

The Pittsburgh Sleep Quality Index (PSQI) was employed, consisting of seven dimensions (0 - 3 points each), giving a total score of 0 - 21; a global score > 7 was defined as sleep disturbance.

2.2.4. Data Analysis

This was performed using SPSS version 27.0. Normally distributed continuous data are expressed as $\bar{x} \pm s$ deviation; pairwise comparisons were performed using independent-samples t-tests, and comparisons among multiple groups were analyzed with one-way analysis of variance (ANOVA). Categorical variables were analyzed by χ^2 test. Correlations were analyzed with Pearson tests. $p < 0.05$ was considered statistically significant.

3. Results

Immunohistochemistry revealed that the mean integral optical density of VIP im-

munoreactivity in the duodenal bulb mucosa was significantly higher in FD patients than in healthy controls, and IL-1β expression demonstrated a comparable up-regulation. Stratification according to Rome III subtypes indicated that expression levels of VIP and IL-1β did not differ significantly among epigastric pain syndrome, postprandial distress syndrome, or the overlap subtype. See Table 1 and Table 2.

Table 1. Comparison of VIP and IL-1β expression levels between the FD group and the control group/ $\bar{x} \pm s$.

Group	Number of cases	IOD/area (VIP)	IOD/area (IL-1β)
Control group	30	0.260 ± 0.092	0.244 ± 0.117
FD group	60	0.347 ± 0.100	0.296 ± 0.074
t	-	3.990	2.225
p	-	<0.001	0.032

Table 2. Comparison of VIP and IL-1β expression levels in different subtypes of FD patients/ $\bar{x} \pm s$.

Group	Number of cases	IOD/area (VIP)	IOD/area (IL-1β)
EPS group	26	0.326 ± 0.109	0.276 ± 0.064
PDS group	24	0.366 ± 0.096	0.309 ± 0.091
Overlap group	10	0.356 ± 0.083	0.315 ± 0.039
F	-	1.061	1.722
p	-	0.353	0.188

3.1. Comparison of PSQI Scores

The total PSQI score in the FD group was 5.983 ± 3.218, significantly higher than that in the control group (3.900 ± 1.517, t = 4.173, p < 0.01). Scores for subjective sleep quality, sleep latency, habitual sleep efficiency, sleep disturbances and use of sleep medication in the FD group were higher than those in controls (p < 0.05), whereas differences in sleep duration and daytime dysfunction were not significant (p > 0.05). See Table 3.

Table 3. Comparison of PSQI scores between the FD group and the control group/ $\bar{x} \pm s$.

Group	Number of cases	Subjective sleep quality	Sleep latency	Sleep duration	Habitual sleep efficiency	Sleep disturbances	Use of sleep medication	Daytime dysfunction	Total score
Control group	30	0.800 ± 0.805	0.867 ± 0.346	0.767 ± 0.679	0.367 ± 0.615	0.667 ± 0.479	0.100 ± 0.305	0.300 ± 0.596	3.900 ± 1.517
FD group	60	1.400 ± 0.995	1.083 ± 0.671	0.783 ± 0.783	0.850 ± 0.732	0.967 ± 0.688	0.400 ± 0.718	0.500 ± 0.701	5.983 ± 3.218
t	-	2.865	2.021	0.099	3.106	2.140	2.775	1.338	4.173
p	-	0.005	0.046	0.921	0.003	0.035	0.007	0.184	<0.001

3.2. Comparison between FD Patients with and without Sleep

Using a PSQI cut-off of >7, FD patients were divided into a pure FD group (n =

44) and an FD-with-sleep-disturbance group (n = 16). The mean IOD/area of VIP in the FD-with-sleep-disturbance group was 0.363 ± 0.099, significantly higher than that in the pure FD group (0.272 ± 0.044, t = 3.566, p < 0.01). The mean IOD/area of IL-1β in the FD-with-sleep-disturbance group was 0.442 ± 0.086, also significantly higher than that in the pure FD group (0.312 ± 0.081, t = 5.381, p < 0.01). See Table 4.

Table 4. Comparison of VIP and IL-1β expression levels between patients with pure FD and patients with FD accompanied by sleep disorders/ $\overline{x} \pm s$.

Group	Number of cases	IOD/area (VIP)	IOD/area (IL-1β)
Pure FD	44	0.272 ± 0.044	0.312 ± 0.081
FD-with-sleep-disturbance	16	0.363 ± 0.099	0.442 ± 0.086
t	-	3.566	5.381
p	-	0.002	<0.001

3.3. Correlation between VIP/IL-1β Expression and PSQI Scores

Pearson correlation analysis showed that VIP expression in the duodenal bulb mucosa was positively correlated with the total PSQI score (r = 0.517, p < 0.01); IL-1β expression was also positively correlated with the total PSQI score (r = 0.557, p < 0.01).

4. Discussion

Previous studies have shown that patients with FD frequently exhibit low-grade inflammatory changes in the duodenal mucosa [12]. This micro-inflammation is closely linked to a variety of neuro-immune mediators, and the proposed mechanism involves the activation of systemic physiological responses via brain-gut axis signalling, ultimately precipitating dyspeptic symptoms [5]. VIP is a neuro-endocrine mediator with well-documented anti-inflammatory properties that also participates in multiple gastrointestinal functions: induction of smooth-muscle relaxation and modulation of duodenal motility; regulation of pancreatic and intestinal secretion; maintenance of ileal basal tone; coordination of colonic smooth-muscle contraction/relaxation, trans-membrane ion transport and mucus secretion; and preservation of the intestinal barrier by promoting epithelial restitution and stabilising tight junctions [13]. IL-1β, in contrast, is involved in a wide spectrum of gastrointestinal pathophysiological processes, including gastric acid output, mucus secretion, mucosal inflammation and neoplastic transformation; its tight regulation is essential for immune homeostasis, whereas excessive activation contributes to the initiation and progression of several gastrointestinal disorders [14]. In the present study, immunohistochemical analysis revealed that VIP and IL-1β expression in the duodenal bulb mucosa was significantly up-regulated in FD patients compared with healthy controls (p < 0.05). This finding is consistent with the elevated duodenal VIP reported by Liang *et al.* [15] in a rat FD model and with the increased duodenal IL-1β expression described by Komori *et al.* [10] in FD

patients. Taken together with previous reports of concomitantly raised serum levels of VIP and IL-1β in FD [16], these data suggest that the inflamed duodenal mucosa may constitute one source of the elevated circulating concentrations of these mediators. Furthermore, VIP and IL-1β expression did not differ among the EPS, PDS or overlap subtypes, indicating that their up-regulation is a shared characteristic of FD rather than a subtype-specific biomarker.

The association between FD and psychosocial factors is now well established. Concurrently, changing lifestyles and increasing psychological stress have led to a rising prevalence of sleep disturbances, whose co-occurrence with FD has attracted considerable attention [17]. In a large multicentre study, Park *et al.* documented sleep disorders in 41.8% of FD patients versus 18.8% of healthy controls ($p < 0.01$), and FD independently increased the risk of sleep impairment by 85% (OR = 1.85 [18]. Nakamura *et al.* prospectively treated 16 FD patients with concomitant sleep disturbance with hypnotics for 4 weeks and observed an 18.4% reduction in PSQI scores, together with 44.1% decreases in mFSSG dyspepsia scores ($p < 0.05$), indicating that pharmacological improvement of sleep can markedly ameliorate gastrointestinal symptoms [19]. These studies have collectively elucidated a robust association between FD and sleep disturbances from diverse perspectives. Nevertheless, conclusive evidence is still lacking to establish the direction of causality—whether FD precipitates sleep disturbances, whether sleep disturbances constitute a predisposing factor for FD, or whether the two conditions are engaged in a bidirectional interplay that mutually exacerbates disease progression. In our cross-sectional survey, FD patients exhibited significantly higher PSQI scores than controls ($p < 0.01$), corroborating the findings of Du *et al.* [20] and reaffirming that diminished sleep quality is a hallmark of the FD phenotype.

IL-1β is capable of crossing the blood-brain barrier or engaging the vagal-solitary tract nucleus-hypothalamic pathway to trigger central inflammatory cascades that disrupt sleep homeostasis. The underlying mechanism involves IL-1β-mediated attenuation of adenosine A1 receptor function in the hypothalamus, a consequent reduction in inhibitory GABAergic neurons' input, and the concomitant activation of the hypothalamic-pituitary-adrenal (HPA) axis; these alterations collectively prolong sleep latency and increase the frequency of nocturnal awakenings. VIP is a pivotal neuropeptide within the suprachiasmatic nucleus (SCN)—the brain's central circadian pacemaker; loss of VIP signalling precipitates circadian disorganisation and abnormal sleep-wake cycles [21]. We observed that FD patients with comorbid sleep disturbance exhibited even higher duodenal VIP and IL-1β expression than those with FD alone ($p < 0.01$), and both mediators correlated positively with PSQI scores ($r = 0.517$ and 0.557, respectively; $p < 0.01$). These data implicate elevated duodenal VIP and IL-1β as potential local neuro-immune correlates of sleep impairment in FD, although whether they functionally bridge the pathophysiological gap between gut inflammation and sleep disruption requires mechanistic validation. Alternatively, sleep disturbances may exacerbate gastrointestinal inflammation via stress-related neuroendocrine pathways. Psycholog-

ical stress could also act as a shared upstream factor, simultaneously influencing mucosal inflammation and sleep quality. Longitudinal studies are needed to disentangle these complex relationships.

5. Limitations of the Study

Our study has limitations. First, serum VIP and IL-1β levels were not measured; consequently, the relationship between mucosal and systemic concentrations remains undefined, and future work should incorporate serological assessments. Second, the cross-sectional design precludes causal inference; longitudinal prospective studies are needed to delineate how temporal changes in duodenal VIP and IL-1β influence sleep quality in FD.

6. Conclusion

The present findings indicate that diminished sleep quality in FD is closely associated with increased duodenal mucosal expression of VIP and IL-1β. These mediators may serve as potential biomarkers for identifying FD patients at risk of sleep disturbances and could represent novel therapeutic targets. For instance, VIP receptor modulators or IL-1β antagonists may warrant exploration in FD patients with comorbid insomnia.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Chen, M.H., Fang, X.C., Hou, X.H., *et al.* (2023) 2022 Expert Consensus on Diagnosis and Treatment of Functional Dyspepsia in China. *Chinese Journal of Gastroenterology*, **28**, 467-481.

[2] Oshima, T. (2024) Functional Dyspepsia: Current Understanding and Future Perspective. *Digestion*, **105**, 26-33. https://doi.org/10.1159/000532082

[3] Oustamanolakis, P. and Tack, J. (2012) Dyspepsia: Organic versus Functional. *Journal of Clinical Gastroenterology*, **46**, 175-190. https://doi.org/10.1097/mcg.0b013e318241b335

[4] Cangemi, D.J. and Lacy, B.E. (2020) Gastroparesis and Functional Dyspepsia: Different Diseases or Different Ends of the Spectrum? *Current Opinion in Gastroenterology*, **36**, 509-517. https://doi.org/10.1097/mog.0000000000000677

[5] Wauters, L., Talley, N.J., Walker, M.M., Tack, J. and Vanuytsel, T. (2020) Novel Concepts in the Pathophysiology and Treatment of Functional Dyspepsia. *Gut*, **69**, 591-600. https://doi.org/10.1136/gutjnl-2019-318536

[6] Hou, X., Yang, D., Yang, G., Li, M., Zhang, J., Zhang, J., *et al.* (2022) Therapeutic Potential of Vasoactive Intestinal Peptide and Its Receptor VPAC2 in Type 2 Diabetes. *Frontiers in Endocrinology*, **13**, Article 984198. https://doi.org/10.3389/fendo.2022.984198

[7] Lima, T.S. (2023) Beyond an Inflammatory Mediator: Interleukin-1 in Neurophysiology. *Experimental Physiology*, **108**, 917-924. https://doi.org/10.1113/ep090780

[8] Wuestenberghs, F., Melchior, C., Desprez, C., Leroi, A., Netchitailo, M. and Gourcerol,

G. (2022) Sleep Quality and Insomnia Are Associated with Quality of Life in Functional Dyspepsia. *Frontiers in Neuroscience*, **16**, Article 829916. https://doi.org/10.3389/fnins.2022.829916

[9] Ali, T. (2013) Sleep, Immunity and Inflammation in Gastrointestinal Disorders. *World Journal of Gastroenterology*, **19**, Article 9231. https://doi.org/10.3748/wjg.v19.i48.9231

[10] Komori, K., Ihara, E., Minoda, Y., Ogino, H., Sasaki, T., Fujiwara, M., *et al.* (2019) The Altered Mucosal Barrier Function in the Duodenum Plays a Role in the Pathogenesis of Functional Dyspepsia. *Digestive Diseases and Sciences*, **64**, 3228-3239. https://doi.org/10.1007/s10620-019-5470-8

[11] Drossman, D.A. (2016) Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV. *Gastroenterology*, **150**, 1262-1279. https://doi.org/10.1053/j.gastro.2016.02.032

[12] Min, Y.W., Lee, H., Ahn, S., Song, K.H., Park, J.K., Shin, C.M., *et al.* (2022) Eosinophil and Mast Cell Counts in the Stomach and Duodenum of Patients with Functional Dyspepsia without a helicobacter Pylori Infection. *The Korean Journal of Gastroenterology*, **80**, 28-33. https://doi.org/10.4166/kjg.2022.036

[13] Jayawardena, D., Guzman, G., Gill, R.K., Alrefai, W.A., Onyuksel, H. and Dudeja, P.K. (2017) Expression and Localization of VPAC1, the Major Receptor of Vasoactive Intestinal Peptide along the Length of the Intestine. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **313**, G16-G25. https://doi.org/10.1152/ajpgi.00081.2017

[14] Zhang, J., Liu, X., Wan, C., Liu, Y., Wang, Y., Meng, C., *et al.* (2020) NLRP3 Inflammasome Mediates M1 Macrophage Polarization and Il-1β Production in Inflammatory Root Resorption. *Journal of Clinical Periodontology*, **47**, 451-460. https://doi.org/10.1111/jcpe.13258

[15] Liang, Q., Yan, Y., Mao, L., Du, X., Liang, J., Liu, J., *et al.* (2018) Evaluation of a Modified Rat Model for Functional Dyspepsia. *Saudi Journal of Gastroenterology*, **24**, 228-235. https://doi.org/10.4103/sjg.sjg_505_17

[16] Liu, L., Yang, W., Lu, Y., Wang, J., Zheng, Y. and Gu, S. (2023) Clinical Efficacy of Tandospirone on Functional Dyspepsia Patients with Anxiety: A Randomized, Placebo-Controlled Study. *Digestive Diseases and Sciences*, **68**, 521-528. https://doi.org/10.1007/s10620-022-07717-z

[17] Huang, Z.P,. Li, S.M., Shen, T., *et al.* (2020) Correlation between Sleep Impairment and Functional Dyspepsia. *Journal of International Medical Research*, **48**, 1-10. https://doi.org/10.1177/0300060520937164

[18] Park, J.K., Huh, K.C., Kwon, J.G., Jung, K.W., Oh, J.H., Song, K.H., *et al.* (2021) Sleep Disorders in Patients with Functional Dyspepsia: A Multicenter Study from the Korean Society of Neurogastroenterology and Motility. *Journal of Gastroenterology and Hepatology*, **36**, 687-693. https://doi.org/10.1111/jgh.15198

[19] Nakamura, F., Kuribayashi, S., Tanaka, F., Kawami, N., Fujiwara, Y., Iwakiri, K., *et al.* ((2021) Impact of Improvement of Sleep Disturbance on Symptoms and Quality of Life in Patients with Functional Dyspepsia. *BMC Gastroenterology*, **21**, Article No. 78. https://doi.org/10.1186/s12876-021-01659-y

[20] Du, H., Lin, R., Xiao, S., Zhao, Y., Wu, M., Chen, W., *et al.* (2023) Improved Sleep Affects Epigastric Pain in Functional Dyspepsia by Reducing the Levels of Inflammatory Mediators. *Digestive Diseases*, **41**, 835-844. https://doi.org/10.1159/000531748

[21] Zhang, Y., Wang, W., Li, J., Zhao, D., Shu, Y., Jia, X., *et al.* (2024) Dexmedetomidine

Accelerates Photoentrainment and Affects Sleep Structure through the Activation of SCNVIP Neurons. *Communications Biology*, **7**, Article No. 1707. https://doi.org/10.1038/s42003-024-07430-9