Melatonin may have a role in the pathogenesis of functional dyspepsia in males

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Abstract. – OBJECTIVE: Pathogenesis of functional dyspepsia (FD) is complex. Melatonin is synthesized in enterochromaffin cells (EC) of the digestive system. It may influence gut function. The aim of this study is to evaluate the serum melatonin levels in FD patients.

PATIENTS AND METHODS: A total of 57 FD patients, and 12 healthy controls were enrolled in this study between 2008-2010 years. Diagnosis of FD was established based on the Rome III Criteria. Blood samples were taken at 10 a.m. and serum samples were stored in -85°C. Serum melatonin levels were determined by an enzyme-linked immunosorbent assay (ELISA) kit. (polyclonal Kennaway G280 anti-melatonin antibody, Bühlmann Laboratories AG, Schönenbuch, Switzerland).

RESULTS: Twenty-three (40.3%) patients were male, and, mean age was 44.3 ± 12.1 years. Mean age of control group was 38.5 ± 11.8 years, and 7 of them were male. The mean serum concentration of melatonin in patients and control group were 31.19 ± 43.4 pg/ml and 14.8 ± 20.9 pg/ml, respectively (p < 0.05). Melatonin levels were significantly higher in male patients (38.6 ± 55 pg/ml vs 12.8 ± 22 pg/ml, p < 0.05). However, melatonin levels were similar in females (p > 0.05).

CONCLUSIONS: The serum melatonin levels were significantly higher in male patients with functional dyspepsia. High nocturnal melatonin secretion may play a role in the pathogenesis of functional dyspepsia, especially in males.

Key Words: Melatonin, Functional dyspepsia, Pathogenesis, Rome III criteria.

Introduction

The functional gastrointestinal disorders (FGIDs) are the most common disorders seen in gastrointestinal (GI) practice. Functional dyspepsia (FD) is defined as the presence of symptoms thought to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms. The pathophysiological determinants of these conditions are related to abnormal motility and visceral hypersensitivity, mucosal immune alterations, and brain-gut dysregulation1. The gut and the brain are highly integrated. According to the biopsychosocial model, GI symptoms can result not only from a diseased or malfunctioning gut, but also from dysregulation at any level of control mechanisms in the gut. This includes the enteric nervous systems, the autonomic neuronal and spinal pathways, and the brainstem and cerebral cortex (i.e. the brain-gut axis)2, 3. Peripheral and central mechanisms are both important in the pathophysiology. Most of the FGIDs share the same pathophysiologic mechanisms but the symptoms are dependent on the affected region.

Melatonin is known as a neurohormone which mainly synthesized in the pineal gland and the gastrointestinal tract. The synthesis of melatonin is regulated by the environmental light/dark cycle via the suprachiasmatic nucleus, and melatonin is mainly secreted at night4. Melatonin plays an important role in various physiological processes, including modulation of circadian rhythms, reproductive system, sleep, body temperature, aging and stimulation of immunity. Melatonin also has oncostatic, antiapoptotic, neuro-protective and cardio-protective effects5,6. It is believed that melatonin produced in the gut acts both as a paracrine molecule and as a hormone released into the portal vein7. The gastroin-
testinal tract is a major source of extrapineal melatonin. It is synthesized in enterochromaffin cells (EC) of the digestive system. In some animals, tissue concentrations of melatonin in the gastrointestinal tract surpass the blood levels by 10-100 times and the digestive tract contributes significantly to melatonin concentrations in the peripheral blood, particularly during the day. A study done by Tasdemir et al\(^8\) demonstrated that significant oxidative and structural changes occurred in rats' brains, spinal cords and testes after pinealectomy but no significant effects were found on the duodenum and stomach. Presence of melatonin in gut suggests that this hormone is somehow involved in digestive pathophysiology. Its paracrine activity may change the motoric and secretory function of gut\(^9\).

Many studies showed that melatonin may have a positive impact on prevention or treatment of colorectal cancer, ulcerative colitis, gastric ulcers, irritable bowel syndrome (IBS), and diarrhea\(^10-14\). Clinical investigations demonstrated that melatonin plays a role mainly in the pathogenesis of upper gastrointestinal tract disorders; much less data have been published on its action in intestinal disorders\(^15\). However, these conditions are controversial. The aim of this study is to evaluate the serum melatonin levels in FD patients.

**Patients and Methods**

A total of 57 patients diagnosed with FD and 12 healthy controls (without any clinical symptoms of digestive disorders) were examined between 2008-2010. Diagnosis of FD was established based on the Rome III criteria\(^16\). Organic gastrointestinal and other disorders were excluded by biochemical, endoscopic and radiologic examinations. Blood samples were taken for examination at 10 a.m. and serum samples were stored in \(-85^\circ\)C. Serum melatonin levels were examined by ELISA (polyclonal Kennaway G280 anti-melatonin antibody, Bühlmann AG, Switzerland).

**Statistical Analysis**

Statistical analysis was performed with SPSS computer software (version 13.0, SPSS Inc, Chicago, IL, USA). Results were presented as mean±SD. Nonparametric Mann-Whitney \(U\) test was used for comparison of both groups. \(p\) values less than 0.05 are accepted as statistically significant (\(p < 0.05\)).

![Figure 1. Melatonin levels in control group and FD patients (\(p < 0.05\)).](image)

![Figure 2. Melatonin levels in males and female patients (\(p < 0.05\)).](image)

**Results**

Fifty-seven patients diagnosed with FD (23 male, 34 female) were enrolled in this study. Mean age of patients was 44.3 ± 12.1 years (range, 18 to 66 years). The control group consisted of 12 healthy participants (7 male, 5 female). Mean age of the control group was 38.5 ± 11.8 years (range, 23 to 55 years). 21 patients and 3 participants in the control group were postmenopausal. The mean serum melatonin levels in FD patients and control group were 31.1 ± 43.4 pg/ml and 14.8 ± 20.9 pg/ml, respectively (\(p < 0.05\)) (Figure-1). Melatonin levels were significantly higher in male patients (38.6 ± 55 pg/ml vs. 12.8 ± 22 pg/ml; \(p < 0.05\)) (Figure 2). However, melatonin levels were similar in females (\(p > 0.05\)) (Table I).
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All patients were questioned for overlapping symptoms of other FGIDs. Forty-two patients were pure FD and didn’t have any overlapping symptoms while 15 (26%) patients had IBS overlapping symptoms. The mean serum melatonin levels were similar in patients with and without overlapping symptoms; 49.4 ± 64 pg/ml and 61.9 ± 7.7 pg/ml, respectively ($p > 0.05$).

Helicobacter pylori was examined in 35 patients; 21 of them (60%) were negative while 14 (40%) were found to be positive. There was no statistically significant difference in mean serum melatonin levels of patients who were negative and positive for Helicobacter pylori (38.47 ± 43 pg/ml and 28.23 ± 53 pg/ml, $p > 0.05$).

Discussion

There are animal studies that show melatonin has inhibitory and excitatory effects on the intestinal motility. In rats, melatonin increased intestinal transit in small dose, but reduced intestinal transit and the force of spontaneous contraction in high concentrations. The mechanisms of melatonin effects on the intestinal motility are not completely elucidated. This study showed that melatonin levels were significantly higher in male FD patients than females. Harasiuk et al. also showed that during the fasting time secretion of melatonin was higher in patients with postprandial distress syndrome compared to healthy subjects. All these findings suggest that FD could be related to high melatonin levels. The absence of significantly high levels in females diagnosed with FD could be related to hormonal differences or differences in the pathogenesis. On the contrary, Klupinska et al. stated that lower nocturnal secretion of melatonin probably may play a role in pathogenesis of upper digestive tract diseases. However, melatonin levels were found higher than controls in our study group, but we did not evaluate nocturnal secretion of melatonin.

Some studies found higher melatonin levels in Helicobacter pylori infected patients when compared to healthy subjects. In our report, melatonin levels were similar in both Helicobacter pylori positive and negative patients.

Melatonin secretion in patients with IBS, especially in patients with constipation dominant IBS, is significantly increased when compared to healthy volunteers. However, in our work melatonin levels were found to be similar in patients with overlap symptoms and the others.

Low number of subjects in patient and control groups could be considered as the main limitation of the present study. However, this study is valuable because there is not too much human studies about melatonin and functional dyspepsia in the literature.

Conclusions

The plasma melatonin levels in males with FD were significantly higher. High nocturnal melatonin secretion may play a role in FD. The absence of significantly high levels in females with FD could be related to hormonal differences. Even though the clinical correlation in males is unknown, this significantly high level needs further studies for the evaluation of pathogenesis and treatment options.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References


