ORIGINAL PAPERS

Adv Clin Exp Med 2006, **15**, 5, 811–815
ISSN 1230-025X

Grażyna Klupińska[1], Agnieszka Harasiuk[1], Cezary Chojnacki[1], Jolanta Jajte[2], Agnieszka Stępień[1], Krystyna Stec-Michalska[1], Jan Chojnacki[1]

Nocturnal Secretion of Melatonin in Patients with Duodenal Ulcer Disease and Ulcer-Like Dyspepsia*

Nocne wydzielanie melatoniny u osób z chorobą wrzodową dwunastnicy i z dyspepsją wrzodopodobną

[1] Department of Gastroenterology and Internal Diseases, Medical University of Łódź, Poland
[2] Department of Toxicology, Medical University of Łódź, Poland

Abstract

Background. Many recent experimental investigations have shown that melatonin has gastroprotective properties. However, its role in the pathogenesis of upper digestive tract diseases is still unclear.
Objectives. Investigating the nocturnal secretion of melatonin in patients with duodenal ulcer or ulcer-like dyspepsia.
Material and Methods. The investigations were carried out in 34 patients with recent duodenal ulcer (DUD), 36 patients with functional ulcer-like dyspepsia (ULD, according to the Rome Criteria II), and in 30 healthy control subjects. Blood samples were taken for examination in a red-lit room at 10 p.m. and then at 2 and 6 a.m. The serum concentration of melatonin was measured with ELISA before and after a six-week treatment with omeprazole (40 mg daily). Patients with *H. pylori* infection additionally took amoxicyllin (2.0 g) and clarithromycin (1.0 g) for seven days.
Results. The average melatonin concentration in duodenal ulcer patients was lower than in the healthy subjects (25.50 ± 6.22 pg/ml and 34.71 ± 4.72 pg/ml, respectively; $p < 0.05$). The highest concentration of melatonin was found in patients with ulcer-like dyspepsia (42.42 ± 9.93 pg/ml, $p < 0.05$). After six weeks, the duodenal ulcers healed and dyspeptic symptoms improved in all patients, but nocturnal secretion had not changed significantly.
Conclusions. The findings suggest that melatonin may play an important role in the pathogenesis of duodenal ulcer disease. In patients with ulcer-like dyspepsia, the influence of melatonin on nocturnal and fasting abdominal pains is also possible (**Adv Clin Exp Med 2006, 15, 5, 811–815**).

Key words: melatonin, duodenal ulcer, ulcer-like dyspepsia.

Streszczenie

Wprowadzenie. Wyniki badań eksperymentalnych wskazują na gastroprotekcyjne działanie melatoniny. Rola tego hormonu w patogenezie chorób górnego odcinka przewodu pokarmowego u ludzi jest mało poznana.
Cel pracy. Ocena wydzielania melatoniny w godzinach nocnych u osób z chorobą wrzodową dwunastnicy i dyspepsją wrzodopodobną.
Materiał i metody. Badania wykonano u 34 osób z czynnym wrzodem dwunastnicy (DUD) i 36 osób z czynnościową dyspepsją wrzodopodobną (ULD) oraz u 30 osób klinicznie zdrowych. Krew do badania pobierano 3-krotnie o godz. 22.00, 2.00 i 6.00, w pokoju oświetlonym wyłącznie światłem czerwonym. Melatoninę w surowicy oznaczano metodą immunoenzymatyczną (ELISA), używając przeciwciał firmy Immuno-Biological Laboratories.
Wyniki. Średnie stężenie melatoniny u osób zdrowych wynosiło 34,71 ± 7,62, u pacjentów z DUD było mniejsze: 25,50 ± 6,22 ($p < 0,05$), a u osób z ULD większe: 42,42 ± 9,93 ($p < 0,05$). Po eradykacji *H. pylori* i 6-tygodniowym leczeniu omeprazolem uzyskano remisję kliniczną DUD i ULD, ale nocne wydzielanie melatoniny nie zmieniło się istotnie.
Wnioski. Uzyskane wyniki podtrzymują wcześniejszą sugestię, że niedobór melatoniny może być jedną z przyczyn wrzodów trawiennych. Nie wykluczają także związku między stężeniem melatoniny we krwi i błonie śluzowej żołądka a występowaniem nocnych bólów brzucha u osób z czynnościową dyspepsją wrzodopodobną (**Adv Clin Exp Med 2006, 15, 5, 811–815**).

Słowa kluczowe: melatonina, choroba wrzodowa dwunastnicy, czynnościowa dyspepsja wrzodopodobna.

* This study was supported by the Medical University of Łódź (grant no. 502-15-303).

Knowledge of the physiological function of melatonin is still incomplete. It has been established that this hormone influences the circadian and seasonal function of endocrine glands, e.g. the pituitary, thyroid, and adrenal glands and the gonads [1]. Melatonin also possesses strong antioxidative properties. As an antioxidative agent it increases the concentration of glutathione (GSH) and the activities of several antioxidative enzymes, including glutathione reductase (GRd), glutathione peroxidase (GPx), and superoxide dismutase (SOD), while inhibiting pro-oxidative enzymes [2, 3]. Recent studies have confirmed the immunomodulatory and anti-inflammatory activity of melatonin [4, 5]. The majority of these observations were made in experimental studies in which melatonin was given in pharmacological doses.

Rather few studies on the gastrointestinal role of melatonin have been carried out in humans. Several investigations concern the evaluation of melatonin's influence on neurological or psychical disturbances and sleeping disorders [6–8]. Recent investigations have provided evidence that melatonin is synthesized not only in the pineal gland, but also in different organs. It was demonstrated that enterochromaffin cells (ECs) in the gut are a source of melatonin and have the capability of absorbing indole components [9]. The total amount of melatonin in the digestive system is much greater than in the pineal gland and the blood [10] and it plays an enteroprotective role in this area. Part of the blood's melatonin probably has its source in the digestive system, especially during the daytime. In the nocturnal hours, melatonin is mainly secreted by the pineal gland, but it may play a gastrointestinal role as well [11].

In previous studies, the present authors found that the nocturnal secretion of melatonin in patients with duoedenal ulcer disease was lower than in healthy individuals [12]. All patients of this group had nocturnal and fasting abdominal pains. Patients with functional acid-like dyspepsia have similar symptoms, but macroscopic changes in the upper digestive tract are not observed. Considering the above, an investigation of the nocturnal secretion of melatonin in both groups of patients was undertaken.

Material and Methods

The investigation was carried out in 34 patients with recent duodenal ulcer, (including 13 women and 21 men, aged 24–51 years) and in 34 patients with ulcer-like dyspepsia (22 women and 14 men, aged 19–43 years). From the clinical perspective, abdominal pain dominated during fasting and at night (8 p.m. – 6 a.m.). Diagnosis of functional dyspepsia was established according to the Rome Criteria II. Organic changes were excluded on the basis of imaging examinations (endoscopy, ultrasonography) and laboratory tests (especially of the liver and pancreas function). *H. pylori* infection was diagnosed by the urea breath test (UBT 13C) and the rapid urease test in 18 patients with duodenal ulcer and in 17 dyspeptic patients. Thirty clinically healthy persons, aged 19–46 years and without *H. pylori* infection, constituted the control group.

Seven days before the examinations the patients were told to abstain from all medications and equal diets were applied. On the day of the investigation the patients remained in a red-lit room at night and received equal liquid diets (NUTRIDRINK, 4 × 200 ml) containing per 100 ml: 8.4 g of carbohydrates, 6 g of proteins, 5.8 g of fat, and vitamins and minerals. Blood samples were taken for examination at 10 p.m. and at 2 a.m. After collection, the blood was centrifuged immediately and frozen in –80°C. The concentration of melatonin was measured by ELISA by using a Labsystems Multiscan and antibodies from Immuno-Biological Laboratories (catalogue no. RE 54021).

The above investigations were carried out before and after a six-week treatment with omeprazole (40 mg daily). Additionally, patients with *H. pylori* received amoxicyllin (2.0 g) and clarithromycin (1.0 g) for seven days.

Written patients consent as well as approval of the Bioethics Committee of the Medical University (RNN 26/04/KB) were obtained.

The Mann-Whitney test chi-squared tests were used for statistical comparisons between groups; $p < 0.05$ was regarded as statistically significant.

Results

The highest concentration of melatonin was determined in all the examined groups at 2 a.m. The healthy subjects' average melatonin level was 53.16 ± 7.02 pg/ml. In patients with duodenal ulcer the secretion of melatonin was statistically lower (34.21 ± 6.54 pg/ml, $p < 0.01$), but in dyspeptic patients higher (62.16 ± 12.14 pg/ml, $p < 0.05$).

At 10 p.m. the concentration of melatonin in duodenal ulcer patients was also lower than in healthy subjects (26.77 ± 6.89 pg/ml and 39.42 ± 11.57 pg/ml, respectively; $p < 0.05$). Their results were similar at 6 a.m. (15.54 ± 5.24 pg/ml and 11.57 ± 4.29 pg/ml, respectively). At 10 p.m. the patients with ulcer-like dyspepsia had a concentration of melatonin similar to that of the control group (39.10 ± 4.24 pg/ml and 39.42 ± 11.57

Table 1. Nocturnal melatonin concentration in the serum of healthy subjects (K) and in patients with duodenal ulcer disease (DUD) and with ulcer-like dyspepsia (ULD)

Tabela 1. Stężenie melatoniny w surowicy w godzinach nocnych u osób zdrowych (K), z chorobą wrzodową dwunastnicy (DUD) i z dyspepsją wrzodopodobną (ULD)

	Melatonin (Melatonina) pg/ml		
Group (Grupa)	10 p.m.	2 a.m.	6 a.m.
K (n = 30)	39.42 ± 11.57	53.16 ± 7.02	11.57 ± 4.29
DUD (n = 34)	26.77 ± 6.89*	34.21 ± 6.54**	15.54 ± 5.24
ULD (n = 36)	39.10 ± 11.10	62.16 ± 12.14*	26.01 ± 6.98*

* $p < 0.05$, ** $p < 0.01$.

pg/ml), but higher at 6 a.m. (26.01 ± 6.98 pg/ml and 11.57 ± 4.29 pg/ml; $p < 0.05$) (Table 1).

The average concentration of melatonin in duodenal ulcer patients was lower (25.50 ± 6.22 pg/ml) and in patients with ulcer-like dyspepsia higher (42.42 ± 10.07 pg/ml) than in the healthy controls (34.71 ± 7.62 pg/ml, $p < 0.05$) (Fig. 1).

During the six weeks of treatment, the clinical symptoms completely subsided. Duodenal ulcers healed in all patients. Eradication of *H. pylori* was obtained in 15 (84.3%) ulcer patients and in 13 (76.5%) patients with ulcer-like dyspepsia. After treatment, the concentration of melatonin in the serum was not significantly changed and was 24.11 ± 4.72 pg/ml in ulcer patients and 39.45 ± 6.24 pg/ml in dyspeptic individuals ($p > 0.05$, Fig. 2)

Discussion

The results confirmed previous observations of these authors indicating lower secretion of nocturnal melatonin in patients with duodenal ulcer disease. In the previous study, melatonin was determined by the RIA method, but in the present examination, using ELISA, comparable results were obtained. These results suggest a possible role of melatonin in the pathogenesis of duodenal ulcer disease. Other investigators express a similar opinion. Komarow et al. [13] observed lower secretion of melatonin in the active phase of duodenal ulcer disease as well as in remission. Moreover, they revealed that the secretion of melatonin is especially depressed in autumn, when progression of this

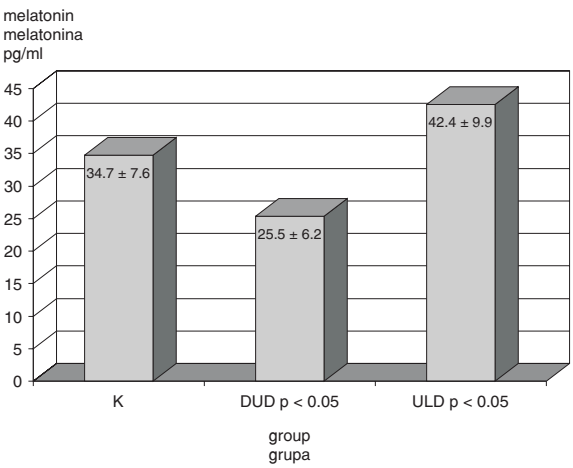

Fig. 1. The average nocturnal melatonin concentration in the serum of healthy subjects (K) and in patients with duodenal ulcer disease (DUD) and with ulcer-like dyspepsia (ULD)

Ryc. 1. Średnie stężenie melatoniny w surowicy w godzinach nocnych u osób zdrowych (K), z chorobą wrzodową dwunastnicy (DUD) i z dyspepsją wrzodopodobną (ULD)

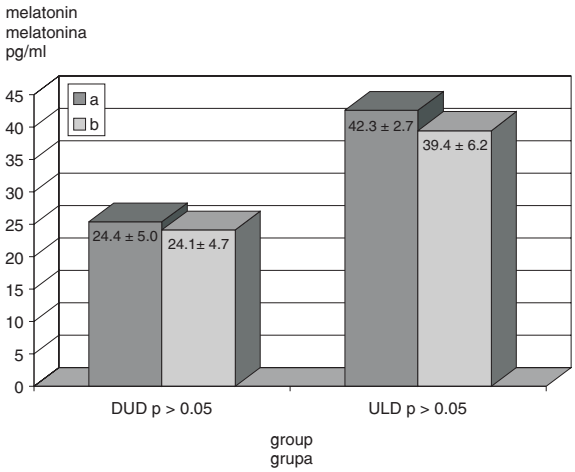

Fig. 2. The average nocturnal melatonin concentration in the serum of patients with duodenal ulcer disease (DUD) and with ulcer-like dyspepsia (ULD) before (a) and after (b) 6 weeks of treatment

Ryc. 2. Średnie stężenie melatoniny w surowicy w godzinach nocnych u osób z chorobą wrzodową dwunastnicy (DUD) i z dyspepsją wrzodopodobną (ULD) przed (a) i po (b) 6 tygodniach leczenia

disease is usually frequent [14]. Malinowskaja et al. [15] observed that the excretion of melatonin with urine is low in every phase of ulcer disease.

The secretion of melatonin at night, when abdominal pains appeared, were investigated in this study because it is possible that a low level of this hormone might be a casual factor in both diseases. Thus melatonin probably induces favorable changes in the activity of the cerebro-visceral axis and reduces visceral hypersensitivity. In particular, its gastroprotective effect is connected with the beneficial influence of the oxygen metabolism in the gastric mucosa and the secretion of prostaglandins. A gastroprotective effect of this hormone has been indicated in numerous experimental investigations [16, 17]. Kato et al. [19] demonstrated a depressed action of melatonin on the secretion of HCL and pepsin. Furthermore, a very important property of melatonin is also its stimulation of bicarbonate secretion. This mechanism is particularly important in the duodenum, where melatonin acts on the MT2 receptors of enterocytes [19]. It has been suggested that melatonin stimulates the duodeno-pancreatic axis and increases the secretion of alkaline pancreatic juice.

All the above properties of melatonin have beneficial influence on the upper digestive tract. Rapaport et al. [20] supported this effect. They observed beneficial changes in the structure of the gastric mucosa in duodenal ulcer patients after melatonin administration.

It is not clear why the secretion of melatonin was not depressed in patients with ulcer-like dyspepsia and with abdominal pains at night. It is likely that a relatively correct secretion of melatonin is comparatively sufficient as an anti-ulcer agent, but is insufficient in the prevention of fasting and nocturnal pain.

References

[1] Reiter RJ: The pineal gland a regulator of regulators. Proc Psychobiol Physiol Psychol 1980, 9, 323–356.

[2] Allegra M, Reiter RJ, Tan D-X, Gentile C, Tesoriere L, Livrea MA: The chemistry of melatonin's interaction with reactive species. J Pineal Res 2003, 34, 1–10.

[3] Reiter RJ, Tan D-X, Mayo JC, Sainz RM, Leon J, Czarnocki Z: Melatonin as an antioxidant: biochemical mechanisms and pathophysiological implications in humans. Acta Bioch Polon 2003, 50, 1129–1146.

[4] Cuzzocrea S, Mazzon E, Serraino I, Lepore V, Terranova ML, Ciccolo A, Caputi AP: Melatonin reduces dinitrobenzene sulfonic acid-induced colitis. J Pineal Res 2001, 30, 1–12.

[5] Guerrero JM, Reiter RJ: Melatonin – immune system relationships. Cur Top Med Chem 2002, 21, 67–179.

[6] Emerit J, Edeas M, Bricaire F: Neurodegenerative diseases and oxidative stress. Biomed Pharmacother 2004, 58, 39–46.

[7] Pacchierotti C, Iapichino S, Bossini L, Pieraccini F, Castrogiovanni P: Melatonin in psychiatric disorders; a review on the melatonin involvement in psychiatry. Front Neuroendocrinol 2001, 22, 18–32.

[8] Wetterberg L: Melatonin and clinical application. Reprod Nutr Dev 1999, 39, 367–382.

[9] Huether G: Melatonin synthesis in the gastrointestinal tract and the impact of nutritional factors on circulating melatonin. Ann NY Acad Sci 1994, 9191, 146–158.

[10] Bubenik GA, Hacker RR, Brown GM, Bartos L: Melatonin concentrations in the luminal fluid, mucosa, and muscularis of the bovine and porcine gastrointestinal tract. J Pineal Res 1999, 26, 56–63.

[11] Otsuka M, Kato K, Murai I, Asai S, Iwasaki A, Arakawa Y: Roles of nocturnal melatonin and the pineal gland in modulation of water-immersion restraint stress-induced gastric mucosal lesions in rats. J Pineal Res 2001, 30, 82–86.

[12] Klupińska G, Malkowski B, Maziarz Z, Chojnacki J, Zając A, Triniszewski W: Nocturnal secretion of melatonin in patients with duodenal ulcer disease. 12th ICE, International Proceedings, Medimond, Bologna 2004, 451–454.

[13] Komarov FI, Rapoport SI, Malinovskaia NK, Voznesenskaia LA, Sharov AA, Vetterberg L: Melatonin production in patients with duodenal ulcer at different stages of disease. Klin Med 1998, 76, 15–18.

[14] Komarov FI, Rapoport SI, Malinovskaia NK, Voznesenskaia LA, Vetterberg L: Melatonin: ulcer disease and seasons of the year. Klin Med 2003, 81, 17–21.

[15] Malinovskaia NK, Komarov FI, Rapoport SI, Voznesenskaia LA, Sharon A, Wetterberg L: Melatonin production in patients with duodenal ulcer. Neuroendocrinol Lett 2001, 22, 109–117.

[16] Brzozowska I, Konturek PC, Brzozowski T, Konturek SJ, Kwiecień S, Pajdo R, Drozdowicz E, Pawlik M, Ptak A, Hahn EG: Role of prostaglandins, nitric oxide, sensory nerves and gastrin in acceleration of ulcer healing by melatonin and its precursor L-tryptophan. J Pineal Res 2002, 32, 149–162.

[17] Brzozowski T, Konturek PC, Konturek SJ, Pajdo R, Bielański W, Brzozowska I, Stachura J, Hahn EG: The role of melatonin and L-tryptophan in prevention of acute gastric lesions induced by stress, ethanol, ischemia and aspirin. J Pineal Res 1997, 32, 79–89.

[18] Kato K, Murai J, Asai S, Takahashi I, Matsuno I, Komuro S, Kurasaka H, Iwasaki A, Isshikawa K, Arakowa Y: Central nervous system action of melatonin on gastric acid and pepsin secretion in pylorus-ligated rats. Neuroreport 1998, 9, 3989–3992.

[19] Sjoblom M, Flemstrom G: Melatonin in the duodenal lumen is a potent stimulant of mucosal bicarbonate secretion. J Pineal Res 2003, 34, 288–293.
[20] Rapoport SI, Raikhlin NT, Malinowskaia NK, Lakshin AA: Ultrastructural changes in cells of the antral gastric mucosa in patients with duodenal ulcers treated with melatonin. Ter Arkh 2003, 75, 10–14.

Address for correspondence:

Grażyna Klupińska
Dept. of Gastroenterology and Internal Diseases
University Hospital No. 5,
Plac Hallera 1,
94-647 Łódź
Poland
tel./fax: +48 42 639 30 49
e-mail: gastro@achilles.wam.lodz.pl

Conflict of interest: None declared

Received: 16.03.2006
Revised: 16.06.2006
Accepted: 21.09.2006

Praca wpłynęła do Redakcji: 16.03.2006 r.
Po recenzji: 16.06.2006 r.
Zaakceptowano do druku: 21.09.2006 r.