JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2020, 71, 6, 817-823
www.jpp.krakow.pl | DOI: 10.26402/jpp.2020.6.05

C. CHOJNACKI[1], T. POPLAWSKI[2], J. BLASIAK[2], M. FILA[3], P. KONRAD[1], J. CHOJNACKI[1]

ALTERED DOPAMINE SIGNALLING IN CHRONIC EPIGASTRIC PAIN SYNDROME

[1]Department of Clinical Nutrition and Gastroenterological Diagnostics, Medical University, Lodz, Poland;
[2]Department of Molecular Genetics, Faculty of Biology and Environmental Sciences, University of Lodz, Lodz, Poland;
[3]Department of Neurology, Polish Mother Memorial Hospital-Research Institute, Lodz, Poland

Chronic epigastric pain syndrome (CEPS) is an important diagnostic problem, especially in patients without macroscopic and microscopic changes in gastric mucosa. The cause of this ailment is unclear. The aim of this study was the assessment of coexistence between symptoms of this syndrome and secretion level of dopamine (DA), as well as the efficacy of peripheral and central D2 receptors antagonist. Sixty depressive patients with CEPS occurring independently of the diet and with no *Helicobacter pylori* infection and 30 healthy subjects were enrolled in this study. Plasma DA and urinary homovanilic acid (HVA) concentration were measured by ELISA, and the mRNA expression of dopa decarboxylase (*DDC*) in gastric mucosa was evaluated by RT-PCR in 30 patients with CEPS and 30 controls. Severity of epigastric pain before and after 12 weeks 2 × 50 mg itopride or sulpiride treatment was evaluated using the modified 10-point Visual Analogue Scale. Higher average levels of plasma DA and urinary HVA levels in CEPS patients than controls 129.5 ± 22.0 versus 109.1 ± 18.4 pg/ml ($p < 0.001$) and 6.82 ± 1.55 versus 5.39 ± 1.04 mg/24 h, respectively were obtained. Moreover, the expression of DDC in gastric mucosa of CEPS patients was higher than in healthy subjects ($p < 0.01$). Sulpiride subsided epigastric pain in 73.3%, but itopride reduced it only in 6.6% of CEPS patients. We concluded that altered dopamine signalling may affect locally-and-centrally mediated chronic epigastric pain.

Key words: *chronic epigastric pain, dopa decarboxylase, dopamine, homovanilic acid, itopride, sulpiride, small intestinal bacterial overgrowth, functional dyspepsia*

INTRODUCTION

Upper gastrointestinal (GI) complaints always provoke a suspicion of a serious organic disease. Chronic and/or recurrent epigastric pain is also a major diagnostic problem. The use of imaging diagnostic methods has shown that even severe GI disorders can occur in the absence of macroscopic and microscopic changes in the gastric mucosa. For this reason, the term functional dyspepsia has been introduced into medical nomenclature, but the criteria for its diagnosis have been changed many times. For many years, *Helicobacter pylori* (*H. pylori*) infection was considered to be the main cause of chronic dyspepsia (1). In 2015 according to the Tokyo Global Consensus, *H. pylori*-associated gastric symptoms were identified as a separate type of dyspepsia (2). However, it is known that in about 80% of patients this infection is asymptomatic (3). On the other hand, eradication of this bacterium does not eliminate dyspeptic symptoms in all patients (4), which indicates the involvement of other factors in the pathogenesis of the disease, including mental aspects (5, 6). The currently applied Rome IV Criteria (7) distinguish two clinical forms of functional dyspepsia: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). In both forms, the complaints are of chronic nature and are related to food intake. EPS patients experience hunger and night pain and their treatment is based mainly on gastric secretion inhibitors (8, 9). In cases in which epigastric pain occurs mainly after meals, prokinetic agents are used in the treatment (10-12). These criteria do not include patients in whom epigastric pain occurs regardless of meals. In the search for causes of gastric pain and discomfort, biologically active agents, mainly serotonin and dopamine (DA), which play a key role in the regulation of GI secretory and motor activity, have been taken into account (11-13). These neurotransmitters are also responsible for the patients psychosomatic state (15, 16). Serotonin stimulates gastric secretion and regulates visceral sensitivity (17). The role of DA, which is found in many structures of the digestive tract, is less understood. It is produced by specific cells of the dopaminergic system, but also by some non-neuronal cells (18, 19). It can also be produced by parietal cells (20) and main cells of gastric glands (21). Dopamine inhibits gastric secretion (22, 23) and is cytoprotective (24). However, a gastroprotective effect was observed after the use of DA receptor antagonists (25). Therefore, DA can display both beneficial and adverse effects in the GI tract, likely depending on its levels and the reactivity of specific receptors. Dopa decarboxylase (*DDC*, aromatic l-amino acid decarboxylase), a major enzyme of the dopaminergic system, catalyzes the decarboxylation of L-3,4-dihydroxyphenylalanine (DOPA) to dopamine, L-5-hydroxytryptophan to serotonin and L-tryptophan to tryptamine. The human *DDC* gene is located on chromosome 7 (7p12.1) and is composed of 15 exons and 14 introns. The expression pattern

of *DDC* is rather complex - alternative splicing events are responsible for the production of seven *DDC* transcripts. Two of them are main "full-length" DDC protein-coding transcripts. DDC is expressed in various tissue and organs including gastric tissue, however, it seems that DDC expression was lower in normal mucosa cells than pathological. *DDC* is also highly polymorphic, more than 25,000 SNP were localized in *DDC* and almost 100 have clinical significance. Taken together *DDC* mRNA expression pattern as well as *DDC* polymorphisms were connected with several human disorders, mainly gastric and colorectal cancers but also neurological diseases, thus they may serve as potential prognostic biomarkers (www.genecards.org).

The aim of this study was the assessment of the DA level and the expression of the *DDC* gene as well as some other features of the dopaminergic system in depressive patients with chronic epigastric pain.

MATERIAL NAD METHODS

Patients

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice (GCP). The approval of Ethics Committee of Medical University in Lodz (RNN -596/11/KB) and patients' written consent were obtained to perform the study.

Sixty subjects in total - 30 patients and 30 controls were enrolled in 2011–2019 in this study. They were 28 – 62 year old (mean age 43.9 ± 14.1 year). The control group consisted of 30 healthy subjects, and 30 patients suffered from chronic epigastric pain syndrome (CEPS) and other complaints, such as early satiety, fullness, nausea, headache and low mental mood. The epigastric pain was continuous, independent on taken meals and had been occurring for at least six months, according to Rome Criteria IV. All subjects underwent through medical examination, including neurological and psychiatric assessment. The mental state were assessed using The Hamilton Depression Rating Scale and following score criteria were adopted: 0 – 7 points - no mental disorders, 8 – 12 - mild depression, 13 – 18 moderate depression, 19 – 29 - severe depression, over 30 point - very severe depression. A thorough medical interview was conducted prior to enrollment in the study, paying attention on the nature of the ailments, their duration, time of day, dependence on meal, their intensity and recurrence. Severity of the pain was evaluated using the modified 10-points Visual Analogue Scale (26). Endoscopic examination of the upper GI tract and histological assessment of gastric and duodenal mucosa were also performed, and no inflammatory changes were found. In order to exclude *H. pylori* infection urea breath test (UBT-13C) was performed using 75 g of labeled urea and FANci-2 system (Thermo Fisher Scientific GmbH, Dreieich, Germany). An increase in breath carbon less than 4.0 ppm was considered a negative results. To exclude small intestinal bacterial overgrowth (SIBO) - lactulose hydrogen breath test (LHBT) was performed using Gastrolyzer (Bedfont Ltd, Harrietsham, UK). According to currently applied criteria, as evidence of absent of SIBO it was considered that the increase in breath hydrogen after administration of 10 g lactulose within 90 minutes was less than 20 ppm.

Exclusion criteria included: *H. pylori* infection, active and atrophic gastritis, as well as eosinophilic and lymphocytic gastritis, peptic ulcer, inflammatory diseases of GI tract, pancreatic and liver disease, small intestinal bacterial overgrowth, allergy and food intolerance, neurological and metabolic diseases, severe depression, use of proton pump inhibitors and psychotropic drugs.

Biochemical and genetic analysis

Routine laboratory examinations included blood cells count, quantification of proteins, glucose, bilirubin, iron, urea, creatinine, C-reactive protein, alanine and asparagine aminotransferase, gamma-glutamyltranspeptidase, amylase and lipase in serum. Samples of gastric mucosa were collected during endoscopy from the body and antrum of stomach. The level of mRNA expression of the *DDC* gene was estimated with RT-PCR, and 50 mg sample of gastric tissue was used in each reaction. Briefly, these samples were rapidly permeated to stabilize and protect cellular RNA with RNA stabilization reagent RNA later® (Qiagen, Hilden, Germany), according to the manufacturer's protocol. The quantity and quality of isolated RNA were estimated spectrophotometrically by Take3 plate on Synergy HT Microplate Reader (BioTek Instruments, Winooski, VT, USA). The real-time gene expression analysis was performed using the TaqMan Gene Expression Assays (Thermo Fisher Scientific, Waltham, MA, USA) with probes for DDC (Assay ID: Hs01105048_m1) with the hypoxanthine phosphoribosyltransferase 1 gene as a reference (assay ID: Hs01003267_m1). Real-time PCR was performed with BioRad CFX96 thermocycler (BioRad, Hercules, CA, USA). Expression analysis was performed with CFX Manager 1.6 software (BioRad). Seven days prior to immunoenzymatic analysis all subjects were on the same diet. On the day of the evaluation all patients were administered the same liquid diet (Nutridrink, Nutricia, Hoofddorp, The Netherlands) in the amount of 3 × 400 ml, containing 18.9 g carbohydrate, 6.0 g protein, 5.8 g lipid/ml, of the total caloric value of 1800 kcal and 1500 ml of isotonic water. Blood samples were drawn in fasting subjects from the antecubital vein at 8:00 a.m. and then they were frozen at –70°C. On the same day, the 14-hour urine collection was taken and the samples were kept at 4°C. Next morning, the volume of urine was measured and the samples were frozen at –70°C. Plasma DA and urinary homovanilic acid concentration were measured by ELISA method with the antibodies RE-59161 (IBL International GmbH, Hamburg, Germany) and HVA 34K01 (Eagle Biosciences, Amherst, NH, USA), respectively. The measurements were performed by photometr at a walvelenght of 450 nm using Expert99 MicroWin 2000 Reader (BMG Labtech GmbH, Ortenberg, Germany). The obtained data were converted from nanogram per mililiter to microgram/24 h.

Therapeutic procedures

After completion of the research the patients were randomly divided into two equal groups and itopride (Zirid-Zentiva) and sulpiride (Sulpiryd-Hasco) at a dose 2 × 50 mg were administrated before breakfast and dinner, for 12 weeks, in an open trial. In this period the patients applied the same balanced diet of total caloric value 1600 kcal and with fenyloalanine intake 35mg/b.w. Diet was prepared using the nutritional calculator with the application Kcalmar.pro-Premium (Hermex, Lublin, Pl). Follow-up medical examinations with the assessment of the relief of symptoms were performed after 4, 8 and 12 weeks.

Statistical analysis

The Mann-Whitney test was used for the comparison of mean value of DDC expression. The correlation between plasma DA level, urinary HVA excretion and severity of epigastric pain was estimated by the Pearson's correlation coefficient with linear regression equation, and the rang Spearman coefficient and Student's t test. Therapeutic effects after prokinetic

treatment was performed using chi-squared test. The Statistica v. 13.3 (StatSoft Inc., Tulsa, OK, USA) software was used to perform statistical analyses.

RESULTS

General characteristic of the subjects enrolled in this study is presented in *Table 1* and *Table 2*.

All patients showed symptoms of mild or moderate depression. Chronic epigastric pain was a main complaint in all examined patients. Other symptoms, as early satiety (96.6% of patients), fullness (90.0%), nausea (81.6%), headache (93.3%), anxiety and depressed mood (76.6%) in different severity were also present.

The expression of DDC in gastric mucosa was higher in CEPS patients than in controls In both the body of stomach and its antral part ($p < 0.01$) (*Fig. 1*).

Plasma DA level in patients was higher than in the control group ($p < 0.001$, *Fig. 2*).

Similarly, urinary HVA excretion in patients was higher than in the control group ($p < 0.001$, *Fig. 3*).

No significant correlation was found between the expression of DDC in gastric mucosa and plasma level and urinary HVA excretion: $r = 0.298$, $p = 0.113$ and $r = 0.253$, $p = 0.180$, respectively.

We found a positive correlation between plasma DA level and severity of epigastric pain ($r = 0{,}757$, $p < 0.001$, *Fig. 4*). The linear dependence between these two values could be estimated by the equation $y = 0.55x + 0.48$.

Table 1. General characteristics of chronic epigastric pain patients and controls with no gastrointestinal complains enrolled in this study.

Feature[a]	**Healthy subjects** (n = 30)	**Patients** (n = 30)
Age (years)	42.6 ± 11.2	45.3 ± 16.9
Gender: Male	6 (20.0%)	13 (43.3%)
Female	24 (80.0%)	17 (56.4%)
HAM-D (points)	4.9 ± 1.3	13.9 ± 3.4***
BMI (kg/m^2)	25.8 ± 1.9	26.5 ± 2.1
RR (mmHg)	127.4 ± 10.6	126.8 ± 8.8

[a]average ± SD; SD, standard deviation; BMI, body mass index; GFR, glomerular filtration rate; HAM-D, Hamilton Depression Rating Scale; RR, blood pressure; statistically significant difference related only to the assessment of mental state. ***$p < 0.001$.

Table 2. Selected laboratory data in healthy subjects and patients with chronic epigastric pain syndrome.

Feature	**Healthy subjects** (n = 30)	**Patients** (n = 30)
RBC (×10$^{6/}$/ml)	4.8 ± 0.23	4.6 ± 0.12
WBC (×10^{12}/l)	6.6 ± 1.8	7.2 ± 2.4
CRP (mg/l)	1.63 ± 1.02	2.23 ± 0.98
Bilirubin (mg/dl)	0.61 ± 0.33	0.82 ± 0.66
ALT (U/l)	19.7 ± 4.7	23.4 ± 2.3
AST (U/l)	18.2 ± 3.1	21.3 ± 4.6
Amylase (U/l)	43.0 ± 12.2	36.4 ± 16.3
Lipase (U/l)	83.2 ± 20.1	36.4 ± 16.3
Creatinine (umol/l)	65.2 ± 12.8	58.6 ± 11.2
GFR (ml/min)	98.6 ± 12.1	95.0 ± 10.6
LHBT (ppm)	12.5 ± 1.9	16.3 ± 6.2

[a]average ± SD; SD, standard deviation; ALT, alanine aminotrasferase; AST, asparagine aminotrasferase CRP, C-reactive protein; GFR, glomerular filtration rate; LHBT, lactulose hydrogen breath test; RBC, red blood cells; WBC, white blood cells; differences between the groups are statistically insignificant.

Table 3. Resolution of ailments after 12-week treatment with itopride (group II a), and with sulpiride (group II b) in patients witch chronic epigastric pain.

Symptoms	**Itopride** (no/%)	**Sulpiride** (no/%)	**chi-square**	**p**
Epigastric pain	2 (6.7)	22 (73.3)	**27.778**	**< 0.001**
Early satiety	21 (70.0)	23 (76.7)	0.341	0.559
Fulness	18 (60.0)	24 (80.0)	2.857	0.091
Nausea	16 (53.3)	21 (70.0)	1.765	0.184
Headache	6 (20.0)	26 (86.7)	**26.786**	**< 0.001**
Mood disorders	8 (26.7)	23 (76.6)	**15.017**	**< 0.001**

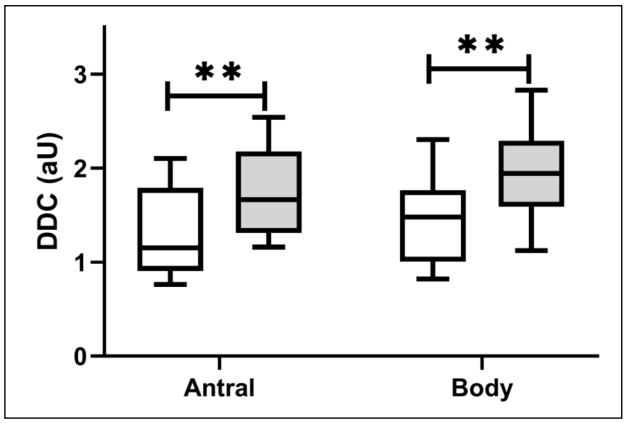

Fig. 1. Relative mRNA expression of dopa decarboxylase (DDC) in antral and body gastric mucosa in healthy subjects (n = 30, white boxes) and patients with chronic epigastric pain (n = 30, grey). Expression was determined by reverse-transcriptase real-time and calculated according to the 2–ΔC formula in arbitrary units (aU) with the hypoxanthine phosphoribosyltransferase 1 gene as a reference. Each measurements was performed in triplicate, median values with first and third quartiles are presented and bars represent 10 and 90 percentiles, **p < 0.01.

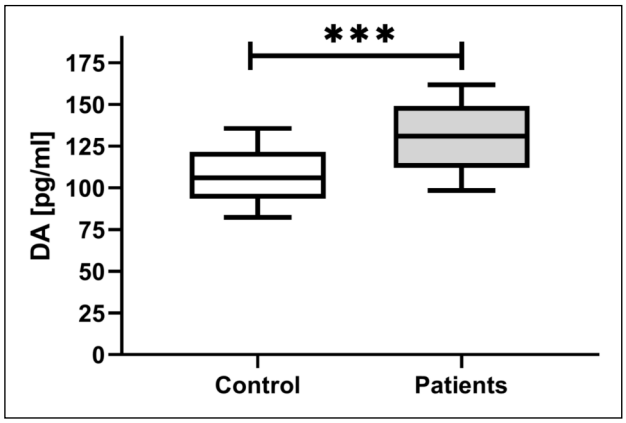

Fig. 2. Plasma dopamine (DA) levels in patients with chronic epigastric pain (n = 30) and healthy controls (n = 30) determined by an ELISA test. Each measurements was performed in duplicate, median values with first and third quartiles are presented and bars represent 10 and 90 percentiles, ***p < 0.001.

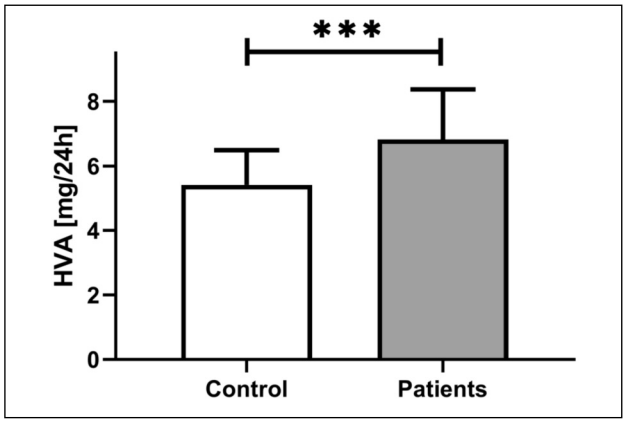

Fig. 3. Urinary homovanilic acid (HVA) excretion patients with chronic epigastric pain (n = 30) and healthy controls (n = 30) determined by an ELISA test. Each measurements was performed in duplicate, mean ± SD, ***p < 0.001.

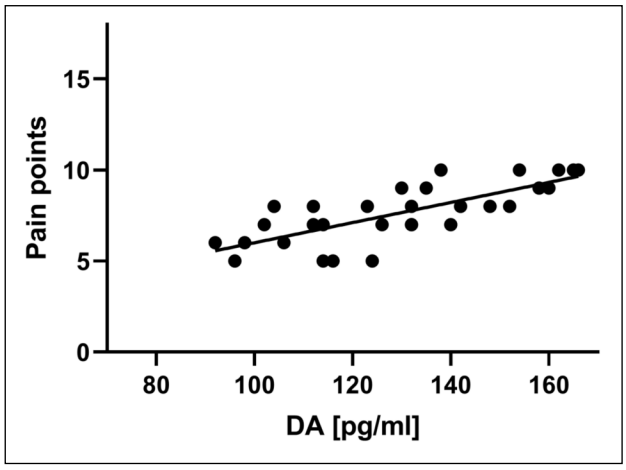

Fig. 4. Correlation between plasma DA level and severity of chronic epigastric pain expressed in points of the Visual Analog Scale. The Pearson correlation coefficient (r) was used to measure the strength of linear correlation between these values.

After 12 weeks epigastric pain subsided in 6.7% of patients treated with itopride, and in 73.3% treated with sulpiride (p < 0.001, *Table 3*).

Similarly, favorable results were also received with regard to headache - 20.0% versus 86.7% (p < 0.001), mood disorders - 26.7% versus 76.6% (p < 0.001). Itopride was well tolerated, while 5 patients (6.0%) used sulpiride reported increased fatigue in the morning in the first week of the treatment, but without the need of therapy termination or dose reduction.

DISCUSSION

The obtained results confirm the previous reports from other laboratories showing the presence of DA synthesizing enzymes in the gastric mucosa, including enteroendocrine cells (18-22). Control of dopa decarboxylase expression at the level of mRNA translation could depend on many factors, and are not statistic, and as the abdominal pain may progresses and resolves so might the function of the dopamine system. In our material the expression of *DDC* was significantly higher in patients with CEPS than in healthy subjects, which may result in an increased DA secretion. It is not known to what extent this affects the secretory and motor activity of the stomach. The role of DA in the pathogenesis of CEPS is unclear. Dopamine may act in autocrine and paracrine manners on local receptors and trigger physiological effects through the serotonin pathway and, after entering the bloodstream, induce endocrine effect (27, 28). The amount of DA produced in the stomach is not very high as compared to other organs. The main sources of plasma DA are nerve and other cells as well as intestinal bacteria and food (29-33). In our study, both the level of DA in blood and the urinary excretion of its metabolite were higher in patients with chronic abdominal pain than in healthy subjects. This might result in the impairment of gastric motility and could trigger dyspeptic symptoms, including early satiety and postprandial discomfort. This is indicated by the disappearance of these symptoms after itopride, which selectively blocks peripheral DA D2 receptors. This drug had no significant effect on abdominal pain and the reduction of which in two patients could be due to the placebo effect. Other authors reported similar results of the treatment of functional dyspepsia with itopride (12, 34). Improvement of postprandial discomfort was also observed after drugs blocking

both peripheral and central D2 receptors (35, 36). Previous our research revealed increased plasma DA levels (37) and the analgesic and antidepressant effects of sulpiride in patients with PDS (38). This indicates the involvement of central dopaminergic centers in the pathogenesis of these ailments. An important role is played by the mesolimbic dopaminergic system, which is responsible for both acute and chronic pain (39), caused especially by anxiety and depression, but this mechanism is poorly understood (40). In clinical practice, I-tetrahydropalmatine (I-TPH) is used, which is D1 receptor agonist and D2 receptor antagonist and has analgesic, sedative and hypnotic effects (41). In our study sulpiride, which blocks peripheral and central nervous system D2 receptors, showed similar effects. This confirms that the pathogenesis of visceral pain and functional gastrointestinal diseases involving neurotransmitters is complex. Many factors, both endogenous and environmental, influence their secretion and activity. Particularly chronic stress changes the homeostasis of many biological processes and disturbs the release and function of neuromodulators, including noradrenaline and DA (42, 43). It leads to a long-term increase of the limbic-hypothalamic-pituitary-adrenal axis activation. In the first period, the excess of these neurotransmitters induces agitation, anxiety and mental and physical discomfort (44). In this phase, various somatic symptoms may appear, including those from the digestive tract, in the form of pain and bloating, constipation or diarrhea, dry mouth and nausea. Excess of catecholamines is also a cause of skin cooling, especially of the hands and feet, headaches and sleep disorders (45). Abdominal pain of psychological nature resembles visceral pain. It arises by irritation of the receptors of afferent fibers of the autonomic system as a result of increased intra-organ pressure (46). Usually it is dull, diffuse, less often colic pain. In the second phase of chronic stress, due to complex changes in the central nervous system, including receptor desensitization, there is a drop in mood, dysthymia and depression. In turn, depression is also a stress for the body and thus the vicious circle of psychosomatic disorders is closed. In the digestive tract, stress and depression lead to further motor dysfunction and to lowering of the visceral sensation threshold (47). These complex changes were the basis for distinguishing centrally mediated abdominal pain syndrome in the Rome Criteria IV.

Pathogenesis of functional dyspepsia and other FGIDSs is still insufficiently known. Many factors related to these disease include abnormalities of gastrointestinal motility and secretion, disturbances of microbiota-gut-brain axis, dysfunction of serotonin signaling, visceral sensitization, psychological factors and other (14, 48-52), but the diagnostic criteria are mainly based on symptoms. Nevertheless, biomarkers are still being sought in order to rationalize therapies. A future treatment option for functional dyspepsia may be the use of ghrelin and its analogues, atypical opiates and other drugs (53, 54).

Our results indicate the main involvement of central factors in the pathogenesis of chronic epigastric pain syndrome. Both itopride and sulpiride alleviated dyspeptic symptoms to a similar degree, but visceral pain resolved mainly after blocking the central D2 receptors. Sulpiride also improved the patients' mood, which confirms the role of DA in the pathogenesis of depression (55, 56). The antidepressant effect of dopaminergic drugs is complex as it manifests itself after both D2 receptor blocking drugs and their agonists (57, 58). These discrepancies depend on dynamic changes in mesolimbic dopaminergic system function, with participation of oligodendrocytes, and DA receptor gene variability (59-61). These changes might play an important role in the pathogenesis of Centrally Mediated Abdominal Pain Syndrome (62). Our study has some limitations, like relatively small number of patients in each group, and like of detailed clinical data before and after treatment with itopride and sulpiride, which point at important elements of further research to explain the mechanisms of the involvement of DA in this syndrome and its psychosomatic aspects.

We conclude that altered dopaminergic signalling may affect locally- and centrally-mediated chronic epigastric pain.

Authors' *contribution*: C. Chojnacki: conceptualization; C. Chojnacki, T. Poplawski, M. Fila: investigation; M. Fila, P. Konrad: carried out the clinical procedures; J. Chojnacki, P. Konrad, J. Blasiak: formal analysis; C. Chojnacki, J. Blasiak, J. Chojnacki: finally designed and realized of the study.

All authors read and approved final manuscript.

Acknowledgments: The authors thank Dr. Alina Knopik-Dabrowicz of Department of Pathomorphology and Cytopathology of Medical Univesity of Lodz for her involvement in cytological study.

Source of funding: The study was supported by the Polish Ministry of Science and Higher Education (NN-4025437/40).

Conflict of interests: None declared.

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Received: December 1, 2020
Accepted: December 30, 2020

Author's address: Prof. Jan Chojnacki, Department of Clinical Nutrition and Gastroenterological Diagnostics, 1 Hallera Square, 90-647 Lodz, Poland.
E-mail: jan.chojnacki@umed.lodz.pl