

Evaluation of serotonin and dopamine secretion and metabolism in patients with irritable bowel syndrome

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Introduction Irritable bowel syndrome (IBS) is the most prevalent functional gastrointestinal disorder with a complex and unclear etiology. It has numerous pathogenic factors, including chronic stress¹ and disorders of intestinal microbiota.² Various preparations are used in the treatment of this condition, but usually without long-lasting outcomes. The diagnosis of IBS is based on the exclusion of organic changes in the gastrointestinal tract; therefore, biochemical markers are still being sought. Changes in the homeostasis of neurotransmitters such as serotonin and dopamine, which are involved in the regulation of all gastrointestinal activities and have a substantial impact on the person's emotional state, are particularly interesting.^{3,4} The aim of this study was to evaluate the secretion and metabolism of serotonin and dopamine in relation to clinical subtypes of IBS.

Patients and methods The study included 98 participants divided into 3 groups: group 1, clinically healthy individuals ($n = 32$); group 2, patients with diarrhea-predominant IBS (IBS-D; $n = 40$); and group 3, patients with constipation-predominant IBS (IBS-C; $n = 36$) with symptom onset at least 6 months prior to the diagnosis. The mean (SD) age of participants in group 1 was 31.9 (8.82) years; in group 2, 32.8 (9.77) years; and in group 3, 33.6 (9.47) years. The diagnosis of IBS was based on Rome IV criteria. All patients enrolled in the study underwent gastroscopy, colonoscopy, histopathologic examination of gastric, duodenal, and colonic mucosa, comprehensive laboratory tests, lactulose hydrogen breath test, and bacteriological stool examination.

The exclusion criteria were as follows: microscopic changes of colonic mucosa; metabolic,

endocrine, and psychiatric disorders; gut inflammatory and autoimmune diseases; food allergy and intolerance; small intestinal bacterial overgrowth; and bacterial and parasitic gastrointestinal infections.

Seven days prior to the study, all medications were withdrawn, and a balanced diet of similar content of tryptophan and phenylalanine was recommended. On the day of the examination, patients remained on a standard liquid diet (Nutridrink, Nutricia Poland, 3×400 ml; isotonic still water, 1500 ml). Blood samples were obtained from an antecubital vein at 8 AM, and 24-hour urine collection was also performed. Serum, plasma, and urine samples were frozen at a temperature of -70°C .

Serum serotonin (Catalog No., RE59121), plasma dopamine (PE59161), and urinary 5-hydroxyindoleacetic acid (5-HIAA; RE59131) and homovanillic acid (HVA; 34K01) levels were determined by an enzyme-linked immunosorbent assay applying IBL antibodies (IBL International GmbH, Hamburg, Germany and Eagle Biosciences, Inc. Nashua, New Hampshire, United States) and Expert 96, MicroWin 2000 S.C. Reader (Biogenet, Józefów, Polska).

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent was obtained from each participant enrolled in the study, and the study protocol was approved by the Bioethics Committee of the Medical University of Lodz (RNN/242/06/KB).

Statistical analysis The nonparametric Kruskal–Wallis test was used to compare the results, and the Mann–Whitney test was used for paired comparisons. Significance of differences was

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TABLE 1 Demographic and laboratory characteristics of the study groups

Parameter	Controls (n = 32)	Patients with IBS-D (n = 40)	Patients with IBS-C (n = 36)	P value
Age, y	31.9 (8.82)	32.8 (9.8)	33.6 (9.5)	>0.05 ^{a,b,c}
Sex, male/female, n (%)	15 (46)/17 (54)	18 (45)/22 (55)	17 (47)/19 (53)	>0.05 ^{a,b,c}
Serotonin, ng/ml	201.2 (34.0)	212.1 (33.6)	140.9 (36.5)	<0.01 ^a >0.05 ^b <0.001 ^c
Dopamine, pg/ml	78.5 (25.7)	77.4 (20.3)	109.3 (18.4)	<0.05 ^{a,c} >0.05 ^b
5-HIAA, mg/24 h	5.25 (1.59)	7.33 (1.68)	5.76 (1.42)	<0.01 ^{a,b} >0.05 ^c
HVA, mg/24 h	6.22 (1.24)	6.68 (1.53)	7.48 (1.75)	<0.05 ^{a,c} >0.05 ^b
5-HIAA/HVA ratio	0.84 (0.24)	1.12 (0.19)	0.78 (0.21)	<0.001 ^a

Data are presented as mean (SD) unless otherwise indicated. A *P* value of less than 0.05 was considered significant.

a IBS-C vs IBS-D; **b** IBS-D vs controls; **c** IBS-C vs controls

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; IBS-C, irritable bowel syndrome with predominant constipation; IBS-D, irritable bowel syndrome with predominant diarrhea

established at a *P* level of less than 0.05. Statistica 9.1 (StatSoft Polska Sp. z o.o., Kraków, Poland) and Microsoft Excel were used for calculations.

Results Controls, patients with IBS-D, and patients with IBS-C did not differ in terms of age and sex (TABLE 1). Differences in laboratory parameters such as serotonin, dopamine, 5-HIAA, and HVA levels, as well as 5-HIAA/HVA ratio between the study groups are presented in detail in TABLE 1.

Discussion The digestive system is a rich source of serotonin (about 90%) in the human body. Serotonin is synthesized mainly in enterochromaffin cells located in all parts of the gastrointestinal tract. These cells are abundant in the large intestine, both in the epithelium and in the glandular part. Tryptophan, an exogenous amino acid, is the substrate of serotonin synthesis. The synthesis involves the participation of tryptophan hydroxylase and 5-tryptophan decarboxylase, as well as 5-HIAA as its final metabolite.⁵ Serotonin stimulates intestinal motility and secretory function by paracrine and endocrine pathways through 5-HT₂, 5-HT₃, and 5-HT₄ receptors.⁶ Its excess, for example, in a carcinoid tumor, causes persistent diarrhea. In physiological states, dopamine (which is secreted by, among others, non-neural cells in the gastrointestinal tract) counteracts excessive stimulation of these activities.⁷ Exogenous phenylalanine and tyrosine are substrates of its synthesis, and tyrosine hydroxylase and aromatic amino acid decarboxylase are the relevant catalyzing enzymes. Dopamine inhibits motor activity and shows antisecretory activity mainly via D₂ receptor. Based on this knowledge, 5-HT₄ tryptamine receptor agonists or 5-HT₃ receptor antagonists,⁸ as well as dopamine D₂ receptor antagonists,⁹ are used in the therapy of

constipation. In IBS-D, 5-HT₃ receptor antagonists have been used; however, due to serious side effects, their administration has been limited.¹⁰ For this reason, new drugs, especially tryptophan hydroxylase inhibitors, are currently under investigation in clinical trials.

Our results indicate that serotonin homeostasis is altered in IBS patients. This confirms that in order to understand functional and inflammatory diseases of the gastrointestinal tract, it is crucial to elucidate the mechanisms of serotonin synthesis and metabolism. Increased serotonin synthesis in the gastrointestinal tract may result from the proliferation of enterochromaffin cells and enhanced activity of synthesizing enzymes. The contribution of nutritional factors is important, including consumed food products containing various amounts of exogenous tryptophan and phenylalanine. This process is also enhanced by inflammatory cytokines⁵ and bacterial metabolites.¹¹ Moreover, some microorganisms can synthesize serotonin and other biologically active compounds,¹² thus maintaining microbial balance in the gastrointestinal tract should also be the target of IBS therapy.

In our patients with IBS-D, the blood levels of serotonin and the urinary levels of its metabolite were significantly higher compared with those in healthy controls and patients with IBS-C. However, patients with IBS-C had higher plasma dopamine and urinary HVA levels. Of note, there were significant differences between IBS groups in the 5-HIAA/HVA ratio, which shows that this parameter may be useful in the differential diagnosis of both types of IBS and other gastrointestinal disorders.

In conclusion, our preliminary results showed that serotonin and dopamine secretion is altered to varying degrees in patients with IBS, which may

determine the type of clinical symptoms. Evaluation of the 5-HIAA/HVA ratio may be a useful noninvasive test in the differential diagnosis of clinical types of IBS. However, further studies are needed to confirm the role of the serotonergic and dopaminergic system in the pathogenesis of IBS and the utility of the 5-HIAA/HVA ratio in its diagnosis.

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