Reduced sodium absorption in the colon under serotonin is a potential factor aggravating secretory diarrhea

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Abstract

Background. Serotonin is a substance with a propulsive effect on the gastrointestinal tract. It stimulates the intestinal secretion of water and electrolytes, and plays an important role in the pathophysiology of secretory diarrhea. However, the influence of serotonin on intestinal absorption is very poorly understood.

Objectives. This study aimed to evaluate the serotonin and selected antagonists of serotonin receptors, i.e., ondansetron (5-HT3) and GR113808 (5-HT4), on electrogenic sodium ion absorption in the colon.

Materials and methods. The electrophysiologic method developed by Ussing and modified with a stimulating function on the mucosal side of the isolated colon wall was used. The influence of selected serotonergic compounds on the electrogenic transport of sodium ions under stationary conditions and mechanical stimulation was investigated. For this purpose, experiments were performed on specimens of isolated rabbit colon. Amiloride and bumetanide were used as reagents directly controlling individual ion transport. The data were analyzed using tests for paired samples (paired sample t-test, Wilcoxon signed-rank test and one-sided sign test).

Results. Serotonin reduced stationary and stimulated colonic sodium absorption. The 5-HT_3 receptor antagonist did not influence the studied phenomenon, while 5-HT_4 antagonists acted contrary to serotonin.

Conclusions. Serotonin reduces both stationary and stimulated sodium ion absorption, thus playing an important role in the pathophysiology of secretory diarrhea. The described phenomenon depends on serotonin's action on 5-HT_4 receptors.

Key words: colon, secretory diarrhea, serotonin, sodium absorption

Cite as
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Background

Intestinal secretion and absorption are complex processes. Their disturbance can lead to constipation or diarrhea. There are many etiological factors causing both disorders, including diseases outside the digestive system. Generally, diarrhea is more dangerous to human life. Although usually a relatively common and mild symptom, it can in some cases be severe and fatal. Regardless of the cause, it is always associated with intestinal malabsorption. The expected amount of water content in the stool of healthy people is approx. 10 mL/kg/day in infants and young children and 200 g/day in adolescents and adults. Diarrhea is the excretion of stool with increased water content, as well as an increased volume, and is manifested by more frequent bowel movements, i.e., 3 or more loose or watery stools a day. Diarrhea creates a risk of both dehydration and dyselectrolytemia regardless of the mechanism.[1,2]

The evaluation in terms of duration distinguishes acute and chronic diarrhea. Acute diarrhea lasts up to 2 weeks and usually has an infectious cause or is associated with a dietary mistake or the use of laxatives. Chronic diarrhea lasts for more than 4 weeks and its etiology is diverse. Although diarrhea is a manifestation of intestinal dysfunction, its primary cause can be completely different and independent of digestive system disorders (e.g., hyperthyroidism, medullary carcinoma of the thyroid, diabetes, systemic mastocytosis, and vagotomy). The majority of diarrhea causes are almost completely understood, but the particular pathophysiological mechanisms involved in the pathogenesis of secretory diarrhea are still being studied.[2,3]

Generally speaking, diarrhea is the result of reduced water absorption or increased water secretion by the intestines. The amount of water in the stool and its appearance is primarily the result of these 2 opposing processes.[2,3] The dominance of intestinal secretion over absorption, which is the leading reason for diarrhea, is usually caused by one of 2 main pathophysiological mechanisms. These include secretory and osmotic factors, thus osmotic and secretory diarrhea can be distinguished from one another.[4,5] Osmotic diarhea occurs due to the presence of osmotically active substances in the intestines, making it difficult to absorb and retain water. Secretory diarrhea results from an increase in active secretion by intestinal epithelial cells.[6] Chloride secretion and related water transport are considered the leading causes of secretory diarrhea and this phenomenon is well known and described in other studies.[3,7–9] Increased chloride secretion is accompanied by a decrease in sodium ion absorption; however, these processes are much less understood. Chloride secretion is aggravated by serotonin (5-hydroxytryptamine (5-HT)). Thus, chloride secretion plays a pivotal role in the pathophysiology of diarrhea when 5-HT production is increased (e.g., in carcinoid tumor). In physiological conditions, 5-HT within the gastrointestinal tract is derived mainly from enterochromaffin cells, but small amounts of 5-HT also come from the neurons of the enteric nervous system.[3,10]

The 5-HT mediates intrinsic and extrinsic neuronal reflexes, stimulates motility, and increases intestinal secretion and vasodilation. There are many disorders causing 5-HT disturbances in the gastrointestinal tract. The most common causes include brain–gut axis disorders, inflammatory bowel diseases and carcinoid syndrome. The clinical symptoms of carcinoid syndrome are mainly caused by its biologically active substance production, the most important being 5-HT. The physiological role of 5-HT in the gastrointestinal tract is disturbed by its overproduction. Normally, the desired 5-HT concentration is sufficient to regulate basic physiological intestine functions, e.g., secretion and motility. Increased 5-HT content intensifies the basic functions of this hormone, causing secretory diarrhea. Despite the well-known influence of 5-HT on secretion in the gastrointestinal tract, its effects on absorption are poorly understood.[3,11–14] Unraveling the pathophysiology of diarrhea allows to search for the most optimal treatment. Thus, our study was designed to discover new mechanisms involved in secretory diarrhea.

Objectives

This study aimed to determine whether 5-HT can affect sodium absorption in the gastrointestinal tract or not. For this purpose, the effects of 5-HT on electrogenic sodium absorption in the isolated distal colon were evaluated. The additional tested substances were 5-HT_3 antagonist (ondansetron) and 5-HT_4 antagonist (GR113808).

Materials and methods

Study design and pharmacological agents

For our study, the basic experimental environment was assured by the transepithelial chloride transport inhibitor (bumetanide). Thus, the measured electrical properties (potential difference and electric resistance) were based on sodium ion transport.[15–18]

The solutions used during experiments (concentration in mmol/L) were:

RF – Ringer fluid (Na 147.2, K 4.0, Ca 2.2, Cl 155.6, Hepes 10.0) buffered to pH 7.4;

AMI – amiloride (0.1) dissolved and diluted with RF;

BUME – bumetanide (0.1) dissolved in dimethyl sulfoxide (0.1%) and diluted with RF;

5-HT – serotonin (0.005) dissolved with BUME;

GR – GR113808 (0.005) dissolved with BUME;

ON – ondansetron (0.005) dissolved with BUME.

Ondansetron, the 5-HT_3 receptor antagonist, was supplied by GlaxoSmithKline (London, UK), while GR113808, the 5-HT_4 receptor antagonist, and other drugs used in this study were supplied by Sigma-Aldrich Ltd., Poznań, Poland.

Animals

The experiments were performed on the distal colon wall isolated from New Zealand white male healthy rabbits weighing 2.5–4.0 kg. There were 10 animals used in the study (3 in the 5-HT group, 3 in the ondansetron group and 4 in the GR113808 group). Before the experiments, the rabbits had unlimited access to water and food. The experiments were approved by Local Committee for Ethical Animal Experiments of the Universities of Bydgoszcz, Poland (approval No. 23/2009).

The preparatory stage

The rabbits were euthanized with isoflurane (4%) dispersed in carbon dioxide. Next, the colonic wall was excised by laparotomy and a 10-cm-long piece was excised from the border of the mesocolon and divided into 4–5 pieces (each about 2.5 cm^2). The pieces were subsequently incubated in BUME and aerated at room temperature for 60 min.

Ussing chamber

For experimental purposes, each colonic specimen was mounted in a Ussing chamber[16–18] filled with a fluid having the same composition as used during the incubation (that is, BUME). The stimulation consisted of gently rinsing the mucosal surface of the examined colonic wall with the experimental fluid through a nozzle connected to a peristaltic pump. The washing nozzle was set at a distance of 2 mm from the mucosa and the rinse was applied using pressure of approx. 6 Pa. Each stimulus lasted 15 s. The experimental procedure was conducted at a temperature of 37°C.

A pair of Ag/AgCl electrodes was used to measure the value of the electric potential difference (PD) between the mucosal and serous surfaces of the isolated colonic wall. The electrodes were connected to an EVC 4000 (World Precision Instruments, Sarasota, USA) amplifier and the data acquisition system MP 100 (Biopack System, Goleta, USA). The system was operated using AcqKnowledge software v. 3.8.1 (Biopack System). The other ends of the electrodes were connected to the half of the Ussing chamber with the agar bridges.

The experiments were always carried out in the same order. The 1st stimulus was BUME (control), while the 2nd were the serotonergic agents dissolved in BUME (the essential part of the experiment). Then, stimulation with BUME was repeated. Next, to inhibit sodium ion transport, AMI was added to the experimental environment alone, and finally AMI with BUME were inserted to obtain a condition with sodium and chloride inhibition. The electrical resistance of the tissue under study was always measured between stimuli.

Statistical analyses

The data were analyzed using tests for paired samples. The Shapiro–Wilk testing allowed to choose the appropriate statistical tool for further evaluation. When the distribution of differences between evaluated couples was normal, a paired sample t-test was used. When the distribution of differences between couples was not normal, non-parametric tests were applied. The Cabilio–Masaro test was used to check if the data were symmetric around the median.[19] When they were symmetric, the Wilcoxon signed rank test was applied. If they were not symmetric, the one-sided sign test was used.

A p-value <0.05 was considered statistically significant. The Cabilio–Masaro formula was calculated using Microsoft Office Excel 2007 (Microsoft Corp., Redmond, USA), while the other experimental data were evaluated using Statistica v. 12 (StatSoft Poland, Kraków, Poland).

Results

There were no excluded animals or experiments. All obtained data were evaluated. The results of the preliminary experiment using GR113808 are shown in Fig. 1. The protocol of test solutions containing different serotonergic agents used in the studies was the same (infusion of drugs was administered in the same order). The stationary transepithelial PD was measured constantly during the experimental period and was negative in relation to the basolateral side. Moreover, it was found that the reaction of isolated colonic wall in a Ussing chamber when gently stimulated with fluid from a peristaltic pump was hyperpolarization (dPD). After the stimulation stopped, the transepithelial PD returned to the baseline conditions, in which the value of the PD was dependent on the use of a serotonergic agent. The results of our statistical analysis are presented in Table 1. Most of the studied results were normally distributed. The statistical analysis of these data was performed using paired t-tests. The distribution of differences between pairs for the electric resistance of bumetanide and 5-HT was symmetric, while the distribution of the potential differences between bumetanide and GR113808 was asymmetric. Therefore, the Wilcoxon test for the 1st analysis and the sign test for the 2nd analysis were used.

Addition of 5-HT (Table 2, Fig. 2) to the fluid washing the mucosal surface of the studied colon caused a reduction in PD and dPD absolute values. The inhibition of the 5-HT_4 receptor (by GR113808) caused opposite effects on 5-HT (Table 3, Fig. 3). Ondansetron, the 5-HT_3

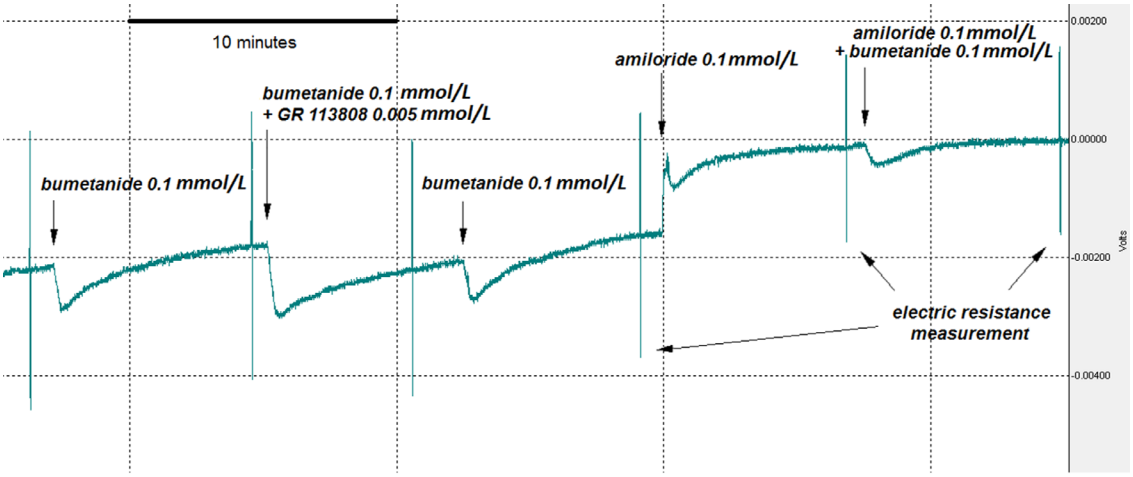

Fig. 1. The course of experimental procedure. Presented example is performed with GR113808 as the tested agent. The vertical arrows indicate the origin of mechanical stimulus. Electrophysiological reaction (dPD) of an isolated colonic wall caused by its mucosal surface stimulation is aggravated by the tested substance (5-HT4 antagonist)

Table 1. Verification of statistical tests assumptions

Variable	n	W_{Sh-W}	p-value	$\|Sk_0\|$	Statistically significant α = 0.05
PD_{B-S}	12	0.967	0.8800	0.56	no
dPD_{B-S}		0.944	0.5573	0.43	no
R_{B-S}		0.6612	0.0004	0.50	no
PD_{B-O}	14	0.943	0.4624	0.25	no
dPD_{B-O}		0.964	0.7937	0.19	no
R_{B-O}		0.891	0.0821	0.08	no
PD_{B-G}	16	0.820	0.0051	1.50	yes
dPD_{B-G}		0.893	0.0630	0.94	no
R_{B-G}		0.901	0.0986	0.56	no

Variables are evaluated differences between means (control compare to the study group). n – number of samples tested consecutively according to the scheme: control compared to the tested substance; W_{Sh-W} and p-value – results of the Shapiro–Wilk test allowing to evaluate data distribution (when $p < 0.05$, then the data distribution is not normal); $|Sk_0|$ – results of the Cabilio–Masaro test allowing to evaluate the symmetry around the median (statistically significant difference for α = 0.05 means asymmetric data distribution); $PD_{B-S, B-O, B-G}$ – differences between paired measurements of transepithelial potential difference for 3 tested groups: bumetanide compared to serotonin, bumetanide compared to ondansetron, bumetanide compared to GR113808, respectively; $dPD_{B-S, B-O, B-G}$ – differences between paired measurements of stimulated transepithelial potential difference for 3 tested groups: bumetanide compared to serotonin, bumetanide compared to ondansetron, bumetanide compared to GR113808, respectively; $R_{B-S, B-O, B-G}$ – differences between paired measurements of electric resistance for 3 tested groups: bumetanide compared to serotonin, bumetanide compared to ondansetron, bumetanide compared to GR113808, respectively.

Table 2. The influence of serotonin on the basic electrical properties of epithelium in the distal colon wall (n = 12)

Variable	Bumetanide (0.1 mmol/L) – control			Serotonin (0.005 mmol/L)		
	PD [mV]	dPD [mV]	R [Ω x cm²]	PD [mV]	dPD [mV]	R [Ω x cm²]
Min	−11.63	−1.83	232	−10.13	−1.23	238
Median	−8.93	−1.37	346	−7.51	−0.82	324
Max	−4.67	−0.73	615	−4.06	−0.34	756
IQR	4.57	0.66	227	3.95	0.48	194
Mean	−7.92	−1.34	382	−7.00	−0.75	385
SE	0.74	0.11	39	0.63	0.08	45
n.d.d.b.m.	–	–	–	yes	yes	no
p-values						
t-test	–	–	–	<0.001	<0.001	–
Wilcoxon test	–	–	–	–	–	0.327

Serotonin (0.005) – dissolved with bumetanide (0.1 mmol/L); Min – minimal value in the data; Max – maximal value in the data; IQR – interquartile range; SE – standard error of the mean; n – number of samples tested consecutively according to the scheme: control compared to the tested substance; PD – transepithelial potential difference; dPD – stimulated transepithelial potential difference; R – electric resistance; n.d.d.b.m. – normal data distribution of the differences between paired measurements (control compared to the study group). The Wilcoxon test was used only when t-test could not been considered (not normal data distribution of the differences) and at the same time data were symmetric around the median (the Cabilio–Masaro test).

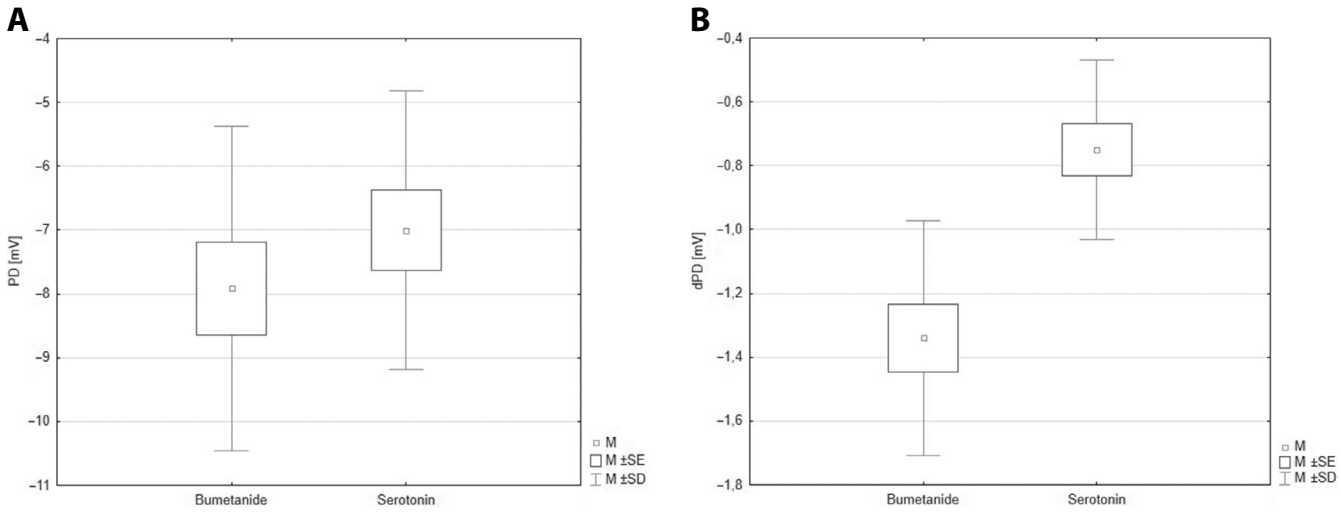

Fig. 2. A. The influence of serotonin on transepithelial electric potential difference (PD) in colon; B. The influence of serotonin on stimulated transepithelial electric potential difference (dPD) in colon

M – mean; SE – standard error; SD – standard deviation.

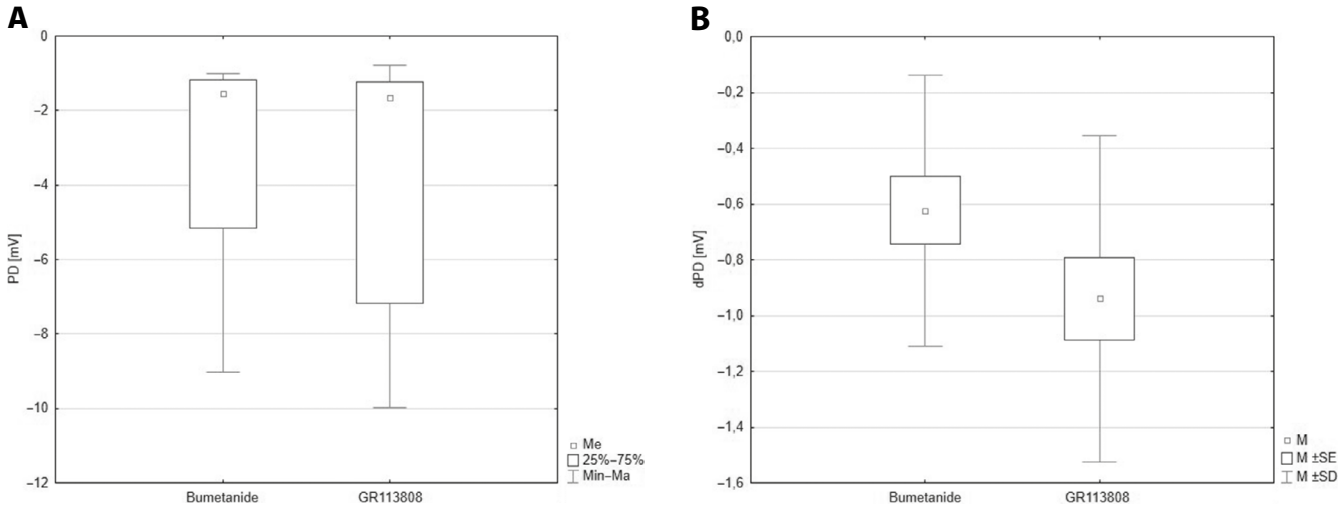

Fig. 3. A. The influence of 5-HT_4 receptor antagonist (GR113808) on transepithelial electric potential difference (PD) in colon; B. The influence of 5-HT_4 receptor antagonist (GR113808) on stimulated transepithelial electric potential difference (dPD) in colon

Me – median; 25%–75% – the range of results in indicated area; Min–Max – the range of minimal and maximal results; M – mean; SE – standard error; SD – standard deviation.

receptor antagonist, did not significantly change any electric properties of the tested specimens (Table 4). The electric resistance was not modified by any of the tested serotonergic drugs.

Discussion

All presented experiments were conducted in an environment with the inhibition of the transepithelial chloride transport; thus, the electric transepithelial PD and its changes were mediated by sodium ion transepithelial flux. Bumetanide used in experiments allowed us to focus on the evaluation of sodium electrogenic transport. The final sequence, with the addition of amiloride to the experimental chamber, confirmed the expected rapid disappearance of the transepithelial electric potential difference.[16]

The 5-HT reduced both the stationary and stimulated absolute values of PD. Thus, 5-HT reduces colonic sodium absorption. The increase in intestinal secretion caused by 5-HT is a well-known phenomenon[3,20–22] and has been confirmed by electrophysiological methods, including the Ussing chamber.[23,24] Studies have reported a reduction in sodium absorption associated with serotonin.[23–25] In the current study, the effects of 5-HT on the reduction of sodium absorption in the large intestine are shown. Subsequently, attempts were made to identify the type of receptor through which the observed reduction of sodium ion transport could be realized. For this study, the antagonists of two 5-HT receptors were also evaluated.

Table 3. The influence of GR113808 (5-HT_4 antagonist) on the basic electrical properties of epithelium in the distal colon wall (n = 16)

Variable	Bumetanide (0.1 mmol/L) – control			GR113808 (0.005 mmol/L)		
	PD [mV]	dPD [mV]	R [Ω x cm^2]	PD [mV]	dPD [mV]	R [Ω x cm^2]
Min	–9.04	–1.67	178	–9.97	–1.92	159
Median	–1.54	–0.40	334	–1.66	–0.86	295
Max	–1.01	–0.23	517	–0.78	–0.27	571
IQR	–3.97	0.63	211	5.95	0.98	298
Mean	–3.17	–0.62	333	–3.87	0.94	341
SE	–0.75	0.12	29	0.89	0.15	39
n.d.d.b.m.	–	–	–	no	yes	yes
p-values						
t-test	–	–	–	–	<0.001	0.775
Wilcoxon test	–	–	–	–	–	–
sign test	–	–	–	0.040	–	–

GR113808 (0.005 mmol/L) – dissolved with bumetanide (0.1 mmol/L); Min – minimal value in the data; Max – maximal value in the data; IQR – interquartile range; SE – standard error of the mean; n – number of samples tested consecutively according to the scheme: control compared to the tested substance; PD – transepithelial potential difference; dPD – stimulated transepithelial potential difference; R – electric resistance; n.d.d.b.m. – normal data distribution of the differences between paired measurements (control compared to the study group). The Wilcoxon test was used only when t-test must not been considered (not normal data distribution of the differences) and data are symmetric around the median (the Cabilio–Masaro test). The one-sided sign test was used for asymmetric data distribution.

Table 4. The influence of ondansetron (5-HT_3 antagonist) on the basic electrical properties of epithelium in the distal colon wall (n = 14)

Variable	Bumetanide (0.1 mmol/L) – control			Ondansetron (0.005 mmol/L)		
	PD [mV]	dPD (mV)	R [Ω x cm^2]	PD [mV]	dPD [mV]	R [Ω x cm^2]
Min	–5.24	–1.94	204	–5.84	–1.92	209
Median	–2.25	–0.75	268	–1.63	–0.72	294
Max	–0.57	–0.23	486	–0.44	–0.29	498
IQR	3.29	0.69	190	3.98	0.83	170
Mean	–2.67	–0.83	321	–2.43	–0.90	335
SE	0.47	0.14	30	0.54	0.15	28
n.d.d.b.m.	–	–	–	yes	yes	yes
p-values (t-test)	–	–	–	0.110	0.233	0.187

Ondansetron (0.005 mmol/L) – dissolved with bumetanide (0.1 mmol/L); Min – minimal value in the data; Max – maximal value in the data; IQR – interquartile range; SE – standard error of the mean; n – number of samples tested consecutively according to the scheme: control compared to the tested substance; PD – transepithelial potential difference; dPD – stimulated transepithelial potential difference; R – electric resistance; n.d.d.b.m. – normal data distribution of the differences between paired measurements (control compared to the study group).

Of all the recognized 5-HT receptors, 5-HT_3 and 5-HT_4 dominate in the intestines and their importance in this section of the gastrointestinal tract is well-known.[26] Thus, antagonists of their activity were tested to determine their 5-HT effects on sodium ion transport.

The primary use of ondansetron and other 5-HT_3 receptor antagonists is for their antiemetic effect.[27] Nevertheless, this group of drugs has been effectively shown to reduce the severity of diarrhea. In clinical trials, 5-HT_3 receptor antagonists reduced diarrhea intensification by influencing intestinal peristalsis and ion transport processes.[28,29] In vitro, studies did not confirm the influence of 5-HT_3 receptor antagonists on intestinal ion transport.[30] The changes caused by 5-HT in the present study were independent also of these receptors.

Experiments using GR113808 confirmed the complete inhibition of 5-HT-induced ion transport under 5-HT_4 receptor blockade.[23] In turn, the stimulation of the 5-HT_4 receptor induces secretion. This phenomenon has been shown with the use of mechanical stimulation on the intestinal mucosa.[31] The participation of 5-HT_4 receptors located on epithelial cells in secretory processes has also been proven.[32]

Limitations

The present study was carried out in vitro and concerned only electrogenic ion transport. Thus, the performed experiments do not reflect all aspects of colonic physiology. However, observed differences should be considered representative of in vivo conditions. Efforts were made to recreate the physiological state as much as possible. For this purpose, several important procedures were

performed. In order to increase the credibility of the results, the experiments were performed at the same time of the day. Since starvation causes disturbances in the transepithelial ion transport and additionally increases the permeability of the intestinal barrier, animals had constant access to water and food until the commencement of euthanasia using isoflurane.[33,34] This gas does not induce permanent changes in transepithelial ion transport and thus does not influence the experimental results.[35,36] It is well known that the mechanisms of ion transport in the rabbit colon and humans are extremely similar; thus, the observed differences are fully representative of humans.[37] In the available literature, numerous publications describe the use of the voltage clamp technique.[9,23,25,30] This form of measurement applies an external electric source to the colon and it is not physiological. In order to achieve a state close to the physiologic environment, a transepithelial electric PD measurement was used.

Conclusions

Mechanical stimulation of colonic mucosa under chloride ion transport inhibition causes an increase in sodium ion absorption processes, manifested by a transient enhancement in the electrical polarity of epithelial tissue. The 5-HT reduces the absorption of sodium in the colon during both mechanical stimulation (dPD) and stationary conditions (PD). Thus, this is one of the implicit mechanisms enhancing 5-HT-dependent secretory diarrhea in vivo. The role of the 5-HT_4 receptor in the described phenomenon concerning sodium absorption has been demonstrated in our study.

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References

1. Surawicz CM. Mechanisms of diarrhea. *Curr Gastroenterol Rep*. 2010; 12(4):236–241. doi:10.1007/s11894-010-0113-4
2. Nemeth V, Pfleghaar N. Diarrhea. In: *StatPearls*. Treasure Island, USA: StatPearls Publishing; 2022. PMID:28846339.
3. Camilleri M, Sellin JH, Barrett KE. Pathophysiology, evaluation, and management of chronic watery diarrhea. *Gastroenterology*. 2017; 152(3):515–532.e2. doi:10.1053/j.gastro.2016.10.014
4. Raman M. Testing for chronic diarrhea. *Adv Clin Chem*. 2017;79:199–244. doi:10.1016/bs.acc.2016.09.004
5. Burgers K, Lindberg B, Bevis ZJ. Chronic diarrhea in adults: Evaluation and differential diagnosis. *Am Fam Physician*. 2020;101(8):472–480. PMID:32293842.
6. Juckett G, Trivedi R. Evaluation of chronic diarrhea. *Am Fam Physician*. 2011;84(10):1119–1126. PMID:22085666.
7. Buddington RK, Wong T, Howard SC. Paracellular filtration secretion driven by mechanical force contributes to small intestinal fluid dynamics. *Med Sci*. 2021;9(1):9. doi:10.3390/medsci9010009
8. Cui Y, Chu F, Yin K, et al. Role of serosal TRPV4-constituted SOCE mechanism in Secretagogues-stimulated intestinal epithelial anion secretion. *Front Pharmacol*. 2021;12:684538. doi:10.3389/fphar.2021.684538
9. Lee B, Hong GS, Lee SH, et al. Anoctamin 1/TMEM16A controls intestinal Cl^- secretion induced by carbachol and cholera toxin. *Exp Mol Med*. 2019;51(8):1–14. doi:10.1038/s12276-019-0287-2
10. Thiagarajah JR, Donowitz M, Verkman AS. Secretory diarrhoea: Mechanisms and emerging therapies. *Nat Rev Gastroenterol Hepatol*. 2015;12(8):446–457. doi:10.1038/nrgastro.2015.111
11. Yang H, Ma T. Luminally acting agents for constipation treatment: A review based on literature and patents. *Front Pharmacol*. 2017;8:418. doi:10.3389/fphar.2017.00418
12. Keating DJ, Spencer NJ. What is the role of endogenous gut serotonin in the control of gastrointestinal motility? *Pharm Res*. 2019;140:50–55. doi:10.1016/j.phrs.2018.06.017
13. Koopman N, Katsavelis D, Ten Hove A, Brul S, de Jonge W, Seppen J. The multifaceted role of serotonin in intestinal homeostasis. *Int J Mol Sci*. 2021;22(17):9487. doi:10.3390/ijms22179487
14. Kanova M, Kohout P. Serotonin: Its synthesis and roles in the healthy and the critically ill. *Int J Mol Sci*. 2021;22(9):4837. doi:10.3390/ijms 22094837
15. Inagaki A, Hayashi M, Andharia N, Matsuda H. Involvement of butyrate in electrogenic K^+ secretion in rat rectal colon. *Pflugers Arch*. 2019;471(2):313–327. doi:10.1007/s00424-018-2208-y
16. Młodzik-Danielewicz N, Tyrakowski T. Effects of amiloride and bumetanide on hyperpolarization after movement across the distal colon epithelium. *Pharmacol Rep*. 2005;57(4):489–497. PMID:16129916.
17. Hołyńska-Iwan I, Bogusiewicz J, Chajdas D, Szewczyk-Golec K, Lampka M, Olszewska-Słonina D. The immediate influence of deltamethrin on ion transport through rabbit skin: An in vitro study. *Pestic Biochem Physiol*. 2018;148:144–150. doi:10.1016/j.pestbp.2018.04.011
18. Hołyńska-Iwan I, Szewczyk-Golec K. Analysis of changes in sodium and chloride ion transport in the skin. *Sci Rep*. 2020;10(1):18094. doi:10.1038/s41598-020-75275-3
19. Cabilio P, Masaro J. A simple test of symmetry about an unknown median. *Can J Statistics*. 1996;24(3):349–361. doi:10.2307/3315744
20. Galligan JJ. Colonic 5-HT_4 receptors are targets for novel prokinetic drugs. *Neurogastroenterol Motil*. 2021;33(4):e14125. doi:10.1111/nmo. 14125
21. Fernandez CJ, Agarwal M, Pottakkat B, Haroon NN, George AS, Pappachan JM. Gastroenteropancreatic neuroendocrine neoplasms: A clinical snapshot. *World J Gastrointest Surg*. 2021;13(3):231–255. doi:10.4240/wjgs.v13.i3.231
22. Gade AK, Olariu E, Douthit NT. Carcinoid syndrome: A review. *Cureus*. 2020;12(3):e7186. doi:10.7759/cureus.7186
23. Ning Y, Zhu JX, Chan HC. Regulation of ion transport by 5-hydroxytryptamine in rat colon. *Clin Exp Pharmacol Physiol*. 2004;31(7):424–428. doi:10.1111/j.1440-1681.2004.04015.x
24. Hardcastle J, Hardcastle PT, Redfern JS. Action of 5-hydroxytryptamine on intestinal ion transport in the rat. *J Physiol*. 1981;320(1):41–55. doi:10.1113/jphysiol.1981.sp013933
25. Hansen MB, Thorbøll JE, Christensen P, Bindslev N, Skadhauge E. Serotonin-induced short-circuit current in pig jejunum. *Zentralbl Veterinarmed A*. 1994;41(1–10):110–120. doi:10.1111/j.1439-0442.1994. tb00073.x
26. Barnes NM, Ahern GP, Becamel C, et al. International union of basic and clinical pharmacology. CX. Classification of receptors for 5-hydroxytryptamine: Pharmacology and function. *Pharmacol Rev*. 2021;73(1): 310–520. doi:10.1124/pr.118.015552
27. Simino GPR, Marra LP, de Andrade EIG, et al. Efficacy, safety and effectiveness of ondansetron compared to other serotonin-3 receptor antagonists (5-HT_3 RAs) used to control chemotherapy-induced nausea and vomiting: Systematic review and meta-analysis. *Exp Rev Clin Pharmacol*. 2016;9(9):1183–1194. doi:10.1080/17512433. 2016.1190271
28. Saslow SB, Scolapio JS, Camilleri M, et al. Medium term effects of a new 5HT_3 antagonist, alosetron, in patients with carcinoid diarrhoea. *Gut*. 1998;42(5):628–634. doi:10.1136/gut.42.5.628
29. Clemens CHM, Samsom M, van Berge Henegouwen GP, Fabri M, Smout AJPM. Effect of alosetron on left colonic motility in non-constipated patients with irritable bowel syndrome and healthy volunteers. *Aliment Pharmacol Ther*. 2002;16(5):993–1002. doi:10.1046/ j.1365-2036.2002.01252.x

30. Frieling T, Wood JD, Cooke HJ. Submucosal reflexes: Distension-evoked ion transport in the guinea pig distal colon. *Am J Physiol Gastrointest Liver Physiol*. 1992;263(1):G91–G96. doi:10.1152/ajpgi.1992.263.1.G91
31. Kellum JM, Albuquerque FC, Stoner MC, Harris RP. Stroking human jejunal mucosa induces 5-HT release and Cl^- secretion via afferent neurons and 5-HT_4 receptors. *Am J Physiol Gastrointest Liver Physiol*. 1999;277(3):G515–G520. doi:10.1152/ajpgi.1999.277.3.G515
32. Kellum JM, Budhoo MR, Siriwardena AK, Smith EP, Jebraili SA. Serotonin induces Cl^- secretion in human jejunal mucosa in vitro via a nonneural pathway at a 5-HT4 receptor. *Am J Physiol Gastrointest Liver Physiol*. 1994;267(3):G357–G363. doi:10.1152/ajpgi.1994.267.3.G357
33. Kosik-Bogacka D, Banach B, Tyrakowski T. Effect of amiloride and bumetanide on ionic currents in the epithelium of caecum from starved rabbits. *Pol J Pharmacol*. 2003;55(2):221–226. PMID:12926550.
34. Kelly P. Starvation and its effects on the gut. *Adv Nutr*. 2021;12(3):897–903. doi:10.1093/advances/nmaa135
35. Tyrakowski T, Smuszkiewicz P, Drobnik L, et al. Effects of halothane and isoflurane on stimulated airway transepithelial ion transport. *Pharmacol Rep*. 2005;57(4):550–555. PMID:16129925.
36. Smuszkiewicz P, Drobnik L, Mieszkowski J, et al. Comparison of the influence of halothane and isoflurane on airway transepithelial potential difference. *Pharmacol Rep*. 2006;58(5):736–745. PMID:17085866.
37. Kunzelmann K, Mall M. Electrolyte transport in the mammalian colon: Mechanisms and implications for disease. *Physiol Rev*. 2002;82(1):245–289. doi:10.1152/physrev.00026.2001