UDC 616.348-002.44-078.092.9
https://doi.org/10.31612/2616-4868.8.2023.11

THE CONTENT OF PROSTANOIDS AND CYCLOOXYGENASES IN COLON TISSUE IN EXPERIMENTAL ULCERATIVE COLITIS

Irina M. Vasylyeva[1], Oksana A. Nakonechna[1], Liudmyla D. Popova[2], Olena V. Solomko[2], Kateryna B. Harbar[3], Natalia V. Yarmysh[1]

1 – Kharkiv National Medical University, Kharkiv, Ukraine
2 – Kyiv Medical University, Kyiv, Ukraine
3 – Private Institution of Higher Education «Kharkiv international Medical University», Kharkiv, Ukraine

Summary

Introduction. The article examines changes in the content of prostaglandins and cyclooxygenases (COX) in colon tissue in ulcerative colitis induced by 2,4-dinitrobenzene sulfonic acid (DNBS) in a 50 % ethanol solution. Based on the obtained results, the authors conclude that changes in the content of the studied parameters, except PGI2, are due to ethanol effect, not DNBS. Both COX isozymes are expressed in normal colon and reduced in ulcerative colitis.
The aim. To study the prostanoids (PGE2, PGI2, PGF2α, TBX2 and 8-iso-PGF2α) and COX-1 and –2 contents in colon tissue in experimental ulcerative colitis.
Materials and methods. The determination of prostanoids and cyclooxygenases contents in colon tissue by enzyme immunosorbent assay was carried out on three groups of sexually mature laboratory rats of both sexes of the WAG population (1st control group – intrarectal injection of saline; 2nd control group – injection of 50 % ethanol; experimental group – injection of DNBS in 50 % ethanol).
Results. PGE2 and PGI2 contents in colon tissue of experimental group rats were statistically significantly higher compared 1st and 2nd control groups. The content of PGE2 was also increased in 2nd control group versus 1st control one. The increasing PGI2 in 2nd control group versus 1st control was not significant. TBX2 and PGF2α contents in experimental and 2nd control groups were significantly lower compared 1st control. 8-iso-PGF2α (non-enzymatically derived prostanoid) level in experimental group rats was significantly higher compared both controls. 8-iso-PGF2α content in 2nd control group was significantly higher compared 1st one. The content of both COX isoforms in colon tissue in experimental group and 2nd control group rats was significantly lower compared to 1st control group.
Conclusions. Both isoforms of COX are expressed in control group colon indicating COX-2 involvement in supporting physiological functions of normal colon tissue. All studied indicators changes, except PGI2, are due to ethanol, not DNBS. Both 50 % ethanol and DNBS in 50 % ethanol stimulate lipid peroxidation, confirmed by significant increase in 8-iso-PGF2α content. PGE2 and PGF2α contents changes against the background of reduced levels of COX-1 and COX-2 in experimental ulcerative colitis are most likely an adaptive response aimed at maintaining colon homeostasis. PGI2 content changes are due to DNBS, and not to ethanol.

Key words: **prostanoids, cyclooxygenase, ulcerative colitis, rats**

INTRODUCTION

Chronic ulcerative colitis and Crohn's disease are the most common inflammatory bowel diseases. Despite intensive research of the causes and pathogenesis of these diseases, the pathogenetic mechanisms of their development have not been elucidated [1].

It is believed that prostanoids are the important players in inflammatory processes [2], but the conclusions of various authors regarding their participation in these processes are contradictory. According to Park Y. S. (2007), endogenous prostanoids are involved in protecting the mucous membrane from colon ulcers during inflammation induced by Dextran sodium sulfate [3]. But according

to results of Lejeune M. et al. (2010), apical exposure of T84 colonic epithelial monolayer to high levels of PGE2 decreased barrier integrity, which was abrogated by an E-prostanoid 4 (EP4) receptor antagonist [4]. In contrast, another study showed that the use of a selective EP4 receptor antagonist, namely rivenprost (ONO-4814), for two weeks for the treatment of patients with mild to moderate ulcerative colitis, significantly improved histological parameters and decreased the index of disease activity [5]. Although PGE_2 and prostacyclin I_2 (PG I_2) may promote inflammatory reactions due to their vasodilating properties, they have antiinflammatory effects by inhibiting the release of reactive oxygen species from neutrophils, preventing mast cell degranulation, inhibiting the formation of a number of other inflammatory mediators [6].

There are few studies on the content of prostanoids in colon tissues in Crohn's disease and ulcerative colitis. Thus, on the model of 2,4,6-trinitrobenzene sulfonic acid (TNBS) – induced colitis in rats Zamuner S. R. et al (2003) showed an increase in PGE_2 synthesis at 1 day and 1 week after TNBS administration and return to basal synthesis level at 2 weeks [7].

According to Martin A. R. et al. (2006) in the mucous membrane of the colon of rats with TNBS-induced colitis (for 14 days) the content of PGE2 was significantly lower compared to the control (administration of saline) [8].

Wei-Guo Dong et al (2003) found elevated levels of PGE2 in two models of colitis in rats (induced with acetic acid – 1 day and TNBS – 7 days) and the degree of increase corresponded to the index of mucosal lesions [9].

Cyclooxygenase is a key enzyme involved in the synthesis of prostanoids. It should be noted that the literature data on the content and role of COX-1 and COX-2 in ulcerative colitis and Crohn's disease are also contradictory [10].

It was previously thought that COX-1 is constitutively expressed in bowel, and COX-2 expression is induced by inflammatory cytokines [10]. This is consistent with the data of Martin A. R. et al (2006), according to which in the mucous membrane of rats with TNBS-induced colitis, the expression of COX-1 did not change, and the expression of COX-2 was significantly higher compared to control [8].

However, there is evidence from the literature that indicates the constitutive expression of COX-2 in the intestine [11]. According to the work of Zielinska A. K. et al (2021), the total activity of COX in the colon in patients with ulcerative colitis and Crohn's disease did not differ from the activity of COX in the control group, but the percentage of COX TG-1 was higher and the percentage of COX-2 was lower than in the control group [12].

Thus, the analysis of literature data indicates the need for further research in this area.

THE AIM

The aim was to study the content of prostanoids (PGE2, PGI2, PGF2α, TBX2 and 8-iso-PGF2α) and cyclooxygenases –1 and –2 in colon tissue in experimental ulcerative colitis.

MATERIALS AND METHODS

Forty-two sexually mature laboratory rats of both sexes of the WAG population, weighing 190-240 g, were used in the work. Animals were kept in standard vivarium conditions. The experimental animals received water and full-rational pelleted feed according to the standards ad libitum. Ulcerative colitis was induced by intrarectal administration of DNBS (10 mg of DNBS dissolved in 250 μl of 50 % ethanol) [13] for 14 days [14, 15].

According to the conditions of the study, the animals were divided into three groups, fourteen animals in each: the first control group consisted of intact animals that were injected with 0.9 % physiological solution; rats of the second control group were injected with a 50 % ethanol solution; rats in the experimental group were injected with DNBS in a 50 % ethanol solution. On the fifteenth day, the animals were removed from the experiment using a guillotine knife.

In colon homogenates, the contents of COX-1, COX-2, PGE2, PGF2α, PGI2, TXB2 were determined by Rat COX-1, Rat COX-2, Rat PGE2, RAT PGF2α, RAT PGI2, RAT TXB2 ELISA Kits (MyBioSource) (USA) and the content of 8-epi-PGF2α by ELISA Kit (Elabscience) (USA) using the Stat Fax 1904 enzyme-linked immunosorbent assay analyzer with tissue pretreatment according to the instructions for the kits.

Statistical data processing was carried out using GraphPad Prism 5 Software (GraphPad Software, USA). Comparisons between two independent groups of variables were performed using a non-parametric Mann–Whitney U test. Results are represented as medians and interquartile ranges. Differences were considered significant at $p<0.05$.

RESULTS

According to the obtained results, PGE2 and PGI2 contents in the colon tissue of rats with DNBS-induced ulcerative colitis were statistically significantly higher compared with the first and the second control groups (Table 1). The PGE2 content was increased by 15.8 % versus 1st control and only by 5 % versus 2nd control; PGI2 – by 17.8 % and 7 % respectively. The content of PGE2 was also increased in 2nd control group versus 1st control one (by 11.28 %, $p<0.001$). The increasing PGI2 in 2nd control group versus 1st control was not significant.

The contents of TBX2 and PGF2α in the experimental group were significantly lower compared 1st control: TBX2 was lower by 82 %, PGF2α – by 74.9 % (Table 1).

The amount of PGF2α in the experimental group rats was higher by 4 % as compared with 2nd control ones (p<0.05). The contents of TBX2 and PGF2α in 2nd control group rats were significantly lower compared with 1st controls: TBX2 was lower by 83 %, PGF2α – by 75.8 % (Table 1).

The sum amount of four investigated prostanoids namely PGE2, PGF2α, PGI2 and TXB2 was significantly diminished in the experimental group (6511 [6320; 7344] pg/g) and 2nd control group (6067 [5842; 6446] pg/g) rats compared to 1st control group (8007 [7382; 9197] pg/g), p<0.001. In the experimental group rats, it was significantly higher compared to 2nd control group (p<0.01).

The level of 8-iso-PGF2α (non enzymatically derived prostanoid) in the experimental group rats was significantly higher compared both controls: by 117 % versus 1st and by 21.7 % versus 2nd ones (Table 1). The content of 8-iso-PGF2α in 2nd control group rats was significantly higher compared 1st control animals (by 78.6 %, p<0.01).

The content of both isoforms of cyclooxygenases in the colon tissue in the experimental group and 2nd control group rats was significantly lower compared to 1st control group (P<0,001): COX-1 content of 2 times, COX-2 content of 3.69 times (Table 2).

Table 1

The content of prostanoids (pg/g of tissue) in the colon of rats with experimental ulcerative colitis (Me [25 %; 75 %])

Prostanoids	1st control group (intrarectal saline injection), n=14	2nd control group (intrarectal 50 % ethanol solution injection), n=14	Experimental group (intrarectal injection of DNBS in 50 % ethanol solution), n=14
PGE2	1906 [1876; 1928]	2121 [2074; 2227]***	2208 [2150; 2302]***, Δ
PGF2α	2497[2378; 2619]	603,6 [588,5; 627,3]***	627,4 [617,5; 639,3]***, Δ
PGI2	2975[2195; 3998]	3295 [2998; 3518]	3505 [3368; 4468]*, Δ
TXB2	648,6[628,1; 680,1]	108,8[103,5; 116,6]***	114,7 [105,1; 130,8]***
8-iso-PGF2α	1802[1754; 1851]	3219 [2931; 3432] **	3917 [3377; 4123]**, Δ

Note: *** – p < 0,001, ** – p < 0,01, * – p < 0,05 in relation to the control with saline; Δ – p<0.05 in relation to the control with ethanol

Table 2

The content of cyclooxygenase 1 and cyclooxygenase-2 in the tissue of the colon in experimental chronic ulcerative colitis (Me [25 %; 75 %])

Groups of animals	Cyclooxygenase-1 (pg/g of tissue)	Cyclooxygenase-2 (ng/g of tissue)
1st control group (intrarectal saline injection), n=14	1343[1324; 1372]	259,2[639,2; 236,0]
2nd control group (intrarectal 50 % ethanol solution injection), n=14	665,3[639,2; 700,6]***	71,82[67,04; 75,35]***
Experimental group (intrarectal injection of DNBS in 50 % ethanol solution)n=14	658,8[640,2; 696,0]***	70,27[68,23; 72,33]***

Note: *** – p < 0,001 in relation to the control with saline

DISCUSSION

It is believed that the prostanoids PGI2 and PGE2 are actively involved in the regulation of homeostasis and basic physiological functions, and during inflammation the synthesis of these two prostanoids increases significantly [16].

According to our results, the contents of PGE2 and PGI2 in the colon tissue of rats with ulcerative colitis were statistically significantly higher compared to both control groups (Table 1), despite the reduced content of COX-1 and COX-2 in this tissue (Table 2).

Cyclooxygenase, a rate-limiting enzyme for the synthesis of prostanoids, including PGE2, PGF2α, PGI2, TXB2, exists in two isoenzyme forms (COX-1 and COX-2). They have different physiological functions and different expression regulation. Cyclooxygenase-1 is constitutively expressed in almost all tissues, and prostanoids produced are involved in the control of homeostatic functions [10]. Data on the basal expression of COX isoenzymes and their role in intestinal pathology are conflicting. Thus, Bjarnoson I. et al (2018) believe that COX-2 is practically not expressed in a healthy intestine [17]. Other authors, on the contrary, point to the constitutive expression of COX-2 in the intestine [11]. According to Fornai M. et al (2006), both COX isoforms are expressed in the normal colon. Moreover, in both normal and inflammatory colon, both isoforms are mainly localized in neurons of the muscular intestinal ganglion [18]. Takeuchi K. and Amagose K. (2018) believe that COX-1 synthesizes prostanoids involved in the protection of the intestinal mucosa, and COX-2 participates in the synthesis of prostanoids involved in the recovery of the affected mucosa [19]. Our results confirm the data on the constitutive expression of COX-2 in the intestine.

Literature data on changes in COX expression and activity in ulcerative colitis and Crohn's disease are also contradictory. That is most likely due to the dependence of COX expression on the stage of the disease and on the type of colon tissue cells studied.

Thus, Gao L. et al. (2021) noted that analysis of publicly available data reveals increased expression of COX-2 in inflamed tissues, especially in stromal cells of the colon, in approximately 60 % of patients with active Crohn's disease or ulcerative colitis [20]. However, as they noted, the expression of COX-2 negatively correlates with the severity of the disease.

According to Porras M. et al. (2005), experiments on rats showed significantly increased expression of COX-2 mRNA in the ileum in the active phase of inflammation and its return to normal in the inactive phase [21].

Gao L. et al. (2021) in a study in mice showed that in response to microbial invasion, resident stromal cells are activated and become the main source of PGE2 during the spread of the disease, but not during the initiation and resolution phases [20].

In experiments on COX-1 and COX-2 knockout mice, it was shown that in 40-50 % of untreated COX-2 (−/-) animals and in Wild-type (wild type) animals after long-term administration of celecoxib (selective COX inhibitor- 2) there was increased permeability and inflammation of the intestine, that indicates the role of COX-2 in maintaining its integrity [22]. According to Takeuchi K. and Amagase K. (2018), inhibition of COX-1 increases the expression of COX-2, that helps maintain the integrity of the mucous membrane, so intestinal damage is observed when both COX-1 and COX-2 are inhibited [19].

It should be noted that the synthesis of all prostanoids is initiated by COX, which catalyzes the conversion of arachidonic acid to PGH2. The total amount of prostanoids of enzymatic origin that we studied was reduced, which is consistent with the obtained data on the decrease in COX levels. Further transformation of PGH2 depends on the ratio of enzymes responsible for the synthesis of specific prostanoids and the level of expression of these enzymes in cells that are the main producers of prostanoids in one or another phase of the disease. In our study, we found a significant decrease in the content of PGF2α (approximately 3 times) in the rats of the experimental group and the second control group compared to the rats of the first control group against the background of a less significant increase in PGE2 (by 15.8 % and 11 %, respectively). This can explain the increase in PGE2 content against the background of COX reduction, considering that PGF2α is synthesized from PGE2. Moreover, the amount of prostanoids depends on the ratio of synthesis and degradation enzymes. It is possible that in these animals the activity of the main enzyme of PGE2 degradation, namely 15-hydroxyprostaglandin dehydrogenase (15-PGDH), is reduced to a greater extent compared to cyclooxygenase. It was shown that the levels of 15-PGDH mRNA and the enzyme itself were significantly reduced in the inflamed mucosa of CD and UC patients [23]. The reduction of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) in IBD provides an additional mechanism for PGE2 increase in those diseases [2].

According to Burakof R. (1990), PGF2α may play an important role in modulating intestinal motility, especially in the distal parts of the colon [24]. PGE2 is known to promote longitudinal muscle contraction and circular muscle relaxation, while PGF2α induces contraction of both muscle layers [25]. Chronic colitis is associated with a decrease in muscle fibers of the colon and loss of mucosal barrier function [26].

COX2 [myeloid cell-specific] KO mice, COX2 [endothelial cell-specific] KO mice, EP4 KO mice (prostaglandin receptor EP4) are more sensitive to DSS colitis [27]. All this emphasizes the importance of COX-2, PGE2 and its receptor EP4 for colonic homeostasis.

The contents of TXB2, a stable metabolite of thromboxane A2 (TXA2), according to our results, in the colon tissue of rats with experimental ulcerative colitis and rats of the second control group were much lower compared to the first control group (table 1). Although in the work of Volkova V. I. (2000) found that in patients with nonspecific ulcerative colitis and Crohn's disease, the content of TXB2 was increased [28], when modeling ulcerative colitis in rats, it was shown that TXB2 increases at the stage of initiation of inflammation, and then decreases significantly [29].

According to our data, the PGI2/TXB2 ratio in rats with induced chronic ulcerative colitis significantly increased, which could have further contributed to the inflammatory response, although the vasoconstrictor effect could be provided not only by thromboxane, but also by 8-epi-prostaglandin F2α, formed nonenzymatically due to activation of lipid peroxidation. It acts mainly through the activation of TXA2 receptors [30].

According to the data obtained, changes in all studied indicators, except PGI2, were due to the «destroyer» of the intestinal barrier ethanol, not the DNBS hapten. The destruction of the intestinal barrier leads to the invasion of intestinal microflora and the initiation of the inflammatory process due to the infiltration of neutrophils and activation of monocytes. That, in turn, is accompanied by the activation of free-radical processes, as evidenced by a significant increase in 8-epi-prostaglandin F2α (table 1), and increased production of IL-1 and TNF-α. Otani T. et al. (2006) showed that TNF-α inhibited the transcription of 15-PGDH and induced COX-2 and microsomal prostaglandin E synthase-1 in human colonocytes, that increased PGE2 synthesis [23].

CONCLUSIONS

Both isoforms of COX are expressed in control group colon indicating COX-2 involvement in supporting physiological functions of normal colon tissue. All studied indicators changes, except PGI2, are due to ethanol, not DNBS. Both 50 % ethanol and DNBS in 50 % ethanol stimulate lipid peroxidation, confirmed by significant increase in 8-iso-PGF2α content. PGE2 and PGF2α contents changes against the background of reduced levels of COX-1 and COX-2 in experimental ulcerative colitis are most likely an adaptive response aimed at maintaining colon homeostasis. PGI2 content changes are due to DNBS, and not to ethanol.

FUNDING AND CONFLICT OF INTEREST

The authors declare no conflict of interest regarding this article. The article is self-funded.

COMPLIANCE WITH ETHICAL REQUIREMENTS

The study design was approved by the Commission of Ethics and Bioethics of the Kharkiv National Medical University. The research was carried out in accordance with the EU Directive 2010/63/EU on the protection of animals used for scientific purposes and the Council of Europe Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS123).

REFERENCES

1. Miao X-P., Ouyang Q., Li H-Y, Wen Z-H., Zhang D-K., Cui X-Y. (2008). Role of selective cyclooxygenase −2 inhibitors in exacerbation of inflammatory bowel disease: a systematic review and meta-analysis. Current Therapeutic Research, 69(3), 181-191. doi:10.1016/j.curtheres.2008.06.009.
2. Dai L., King D., Perera D. S., Lubowski D. Z., Burcher E., Liu L. (2015). Inverse expression of prostaglandin E2-related enzymes highlights differences between diverticulitis and inflammatory bowel disease. Dig Dis Sci., 60(5), 1236-46. doi: 10.1007/s10620-014-3478-7.
3 Park Y.S. (2007). COX-2 inhibitors in inflammatory bowel disease: friends or foes?, Korean J Gastroenterol., 50 (6), 350-355. PMID: 18159171
4. Lejeune M., Leung P., Beck P. L., Chadee K. (2010). Role of EP4 receptor and prostaglandin transporter in prostaglandin E2-induced alteration in colonic epithelial barrier integrity. Am J Physiol Gastrointest Liver Physiol., 299(5), G1097-105. doi: 10.1152/ajpgi.00280.2010
5. Nakase H, Fujiyama Y, Oshitani N, Oga T, Nonomura K, Matsuoka T, Esaki Y, Murayama T, Teramukai S, Chiba T, Narumiya S. (2010). Effect of EP4 agonist (ONO-4819CD) for patients with mild to moderate ulcerative colitis refractory to 5-aminosalicylates: a randomized phase II, placebo-controlled trial, Inflamm Bowel Dis., 16(5), 731-3. doi: 10.1002/ibd.21080
6. Ajuebor M. N., Singh A., Wallace J. L. (2000). Cyclooxygenase-2-derived prostaglandin D(2) is an early anti- inflammatory signal in experimental colitis. Am J Physiol Gastrointest Liver Physiol., 279(1), G238-44. doi: 10.1152/ajpgi.2000.279.1.G238.
7. Zamuner S. R., Warrier N., Buret A. G., MacNaughton W. K, Wallace J. L. (2003). Cyclooxygenase 2 mediates post-inflammatory colonic secretory and barrier dysfunction. Gut., 52, 1714-1720. doi10.1136/gut.52.12.1714
8. Martín A. R., Villegas I., Sánchez-Hidalgo M., de la Lastra C. A. (2006).The effects of resveratrol, a phytoalexin derived from red wines, on chronic inflammation induced in an experimentally induced colitis model. Br J Pharmacol., 147(8), 873-885. doi: 10.1038/sj.bjp.0706469
9. Dong WG., Mei Q., Yu JP, Xu JM, Xiang L., Xu Y. (2003). Effects of melatonin on the expression of iNOS and COX-2 in rat models of colitis. World J Gastroenterol, 9 (6), 1307-1311. doi: 10.3748/wjg.v9.i6.1307
10. Maseda D., Ricciotti, E. (2020). NSAID-Gut Microbiota Interactions. Front Pharmacol, Aug 7:11 11, 1153. doi: 10.3389/fphar.2020.01153.
11. Kirkby N. S., Chan M. V., Zaiss A. K., Garcia-Vaz E., Jiao J., Berglund L. M., Verdu E. F., Ahmetaj-Shala B., Wallace J. L., Herschman H. R., Gomez M. F., Mitchell J. A. (2016). Systematic study of constitutive cyclooxygenase-2 expression: Role of NF-κB and NFAT transcriptional pathways. Proc. Natl. Acad. Sci. USA, Dec 28, 113 (2), 434-439. doi: 10.1073/pnas.1517642113
12. Zielińska A. K., Sałaga M., Siwiński P., Włodarczyk M., Dziki A., Fichna J. (2021). Oxidative Stress Does Not Influence Subjective Pain Sensation in Inflammatory Bowel Disease Patients. Antioxidants (Basel), 10(8), 1237. doi: 10.3390/antiox10081237
13. Wallace, J.L., Le. T., Carter, L., Appleyard, C.B., & Beck, P.L. (1995). Hapten-induced chronic colitis in the rat: Alternatives to trinitrobenzene sulfonic acid. J. Pharmacol. Toxicol. Methods, 33(4), 237-239. DOI: 10.1016/1056-8719(95)00001-x
14. Sanovic S., Lamb D. P., Blennerhassett M. G. (1999). Damage to the Enteric Nervous System in Experimental Colitis. The American Journal

of Pathology, 155(4), 1051-1057. doi: 10.1016/S0002-9440(10)65207-8
15. Morampudi V., Bhinder G., Wu X., Dai C., Sham Ho P., Vallance B. A., Jacobson R. (2014).DNBS/TNBS colitis models: providing insights into inflammatory bowel disease and effects of dietary fat. J. Vis. Exp., 27(84), e51297. doi: 10.3791/51297
16. Norel X., Sugimoto Y., Ozen G., Abdelazeem H., Amgoud Y., Bouhadoun A., Bassiouni W., Goepp M., Mani S., Manikpurage H., Senbel A., Longrois D., Heinemann A., Yao C., Clapp L. H. (2020). International Union of Basic and Clinical Pharmacology. CIX. Differences and Similarities between Human and Rodent Prostaglandin E2 Receptors (EP1-4) and Prostacyclin Receptor (IP): Specific Roles in Pathophysiologic Conditions. Pharmacol Rev., 72(4), 910-968. doi: 10.1124/pr.120.019331.
17. Bjarnason I., Scarpignato C., Holmgren E., Olszewski M., Rainsford K. D., Lanas A. (2018). Mechanisms of Damage to the Gastrointestinal Tract From Nonsteroidal Anti-Inflammatory Drugs. Gastroenterology, 154, 500-514. 10.1053/j.gastro.2017.10.049
18. Fornai M., Blandizzi C., Antonioli L., Colucci R., Bernardini N., Segnani C., De Ponti F., Tacca G. M. (2006). Differential role of cyclooxygenase 1 and 2 isoforms in the modulation of colonic neuromuscular function in experimental inflammation. J Pharmacol Exp Ther., 317, 938-945. doi:10.1124/jpet.105.098350
19. Takeuchi K., Amagase K. (2018). Roles of Cyclooxygenase, Prostaglandin E2 and EP Receptors in Mucosal Protection and Ulcer Healing in the Gastrointestinal Tract. Curr. Pharm., 24 (18), 2002-2011. doi: 10.2174/1381612824666180629111227
20. Gao L, Yu Q, Zhang H, Wang Z, Zhang T, Xiang J, Yu S, Zhang S, Wu H, Xu Y, Wang Z, Shen L, Shu G, Chen YG, Liu H, Shen L, Li B. (2021). A resident stromal cell population actively restrains innate immune response in the propagation phase of colitis pathogenesis in mice. Sci Transl Med., Jul 21, 13(603), eabb5071. doi: 10.1126/scitranslmed.abb5071.
21. Porras M., Martín M. T., Torres R., Vergara P. (2006). Cyclical upregulated iNOS and long-term downregulated nNOS are the bases for relapse and quiescent phases in a rat model of IBD. Gastrointestinal and Liver Physiology, 290(3), G423-430. doi.org/10.1152/ajpgi.00323.2005
22. Sigthorsson G., Simpson R. J., Walley M., Anthony A., Foster R., Hotz-Behoftsitz Ch., Palizban A., Pombo J., Watts Jo, Morham S. G., Bjarnason, I. (2002). COX-1 and 2, intestinal integrity, and pathogenesis of nonsteroidal anti-inflammatory drug enteropathy in mice. Gastroenterology, 122 (7), 1913-1923. doi: 10.1053/gast.2002.33647.
23. Otani T., Yamaguchi K., Scherl E., Du B., Tai H. H., Greifer M., Petrovic L., Daikoku T., Dey S. K., Subbaramaiah K., Dannenberg A. J. (2006). Levels of NAD(+)-dependent 15 – hydroxyprostaglandin dehydrogenase are reduced in inflammatory bowel disease: evidence for involvement of TNF-alpha. Am J Physiol Gastrointest Liver Physiol, 290(2), G. 361-368. doi: 10.1152/ajpgi.00348.2005
24. Burakoff R., Nastos E., Won S. (1990). Effects of PGF2 alpha anGasd of indomethacin on rabbit small and large intestinal motility in vivo. Gastrointestinal and Liver Physiology, 258 (2), G231-237. doi.org/10.1152/ajpgi.1990.258.2.G231
25. Park C. G., Kim Y. D., Kim M. Y., Koh J. W., Jun J. Y., Yeum C. H., So I., Choi S. (2011). Effects of prostaglandin F2α on small intestinal interstitial cells of Cajal. World J Gastroenterol, 17(9), 1143-1151. doi: 10.3748/wjg.v17.i9.1143
26. Safdari B. K., Sia T. C., Wattchow D. A., Smid S. D. (2016). Effects of proinflammatoty cytokines, lipopolysaccharide and COX-2mediators on human colonic neuromuscular function and epithelial permeability. Cytokine, 83, 231-238. doi: 10.1016/j.cyto.2016.04.017.
27. Mizoguchi A. (2012). Animal Models of Inflammatory Bowel Disease. Atsushi Mizoguchi Progress in Molecular Biology and Translational Science, 105, 263-320. https://doi.org/10.1016/B978-0-12-394596-9.00009-3
28. Volkov V. I. (2000). Activity of the prostanoids system in inflammatory diseases of the colon. Klin Khir., 10, 30-1. PMID: 11247426
29. Hamabata T., Nakamura T., Masuko S., Maeda S., Murata T. (2018). Production of lipid mediators across different disease stages of dextran sodium sulfate-induced colitis in mice. J Lipid Res., 59, 586-595. doi:10.1194/jlr.M079095.
30. Takahashi K., Nammour T. M., Fukunaga M., Ebert J., Morrow J.D, Roberts L. J., Hoover R. L., Badr K. F. (1992). Glomerular actions of a free radical-generated novel prostaglandin, 8-epi-prostaglandin F2 alpha, in the rat. Evidence for interaction with thromboxane A2 receptors. J Clin Invest., 90(1), 136-141. https://doi.org/10.1172/JCI115826

Резюме

ВМІСТ ПРОСТАНОЇДІВ ТА ЦИКЛООКСИГЕНАЗ В ТКАНИНІ ТОВСТОЇ КИШКИ ПРИ ЕКСПЕРИМЕНТАЛЬНОМУ ВИРАЗКОВОМУ КОЛІТІ

Ірина М. Васильєва[1], Оксана А. Наконечна[1], Людмила Д. Попова[2], Олена В. Соломко[2], Катерина Б. Гарбар[3], Наталія В. Ярмиш[1]

1 – Харківський національний медичний університет, м. Харків, Україна
2 – Київський медичний університет, м. Київ, Україна
3 – Приватний вищий навчальний заклад «Харківський міжнародний медичний університет», м. Харків, Україна

Вступ. У статті досліджено зміни вмісту простагландинів та циклооксигеназ (ЦОГ) в тканині товстої кишки при виразковому коліті, індукованому 2,4-Dinitrobenzenesulfonic acid (DNBS) у 50 % розчині етанолу. На підставі отриманих результатів автори роблять висновок, що зміни вмісту досліджених параметрів, за виключенням PGI2, обумовлені дією етанолу, а не DNBS. Обидві ізоферменті форми ЦОГ експресуються в тканині товстої кишки за нормальних умов та знижуються при виразковому коліті.
Мета. Визначити вміст простаноїдів (PGE2, PGI2, PGF2α, TBX2 та 8-ізо-PGF2α) та ЦОГ-1 та –2 у тканині товстої кишки при експериментальному виразковому коліті.
Матеріали та методи. На трьох групах статевозрілих лабораторних щурів обох статей популяції WAG (перша контрольна група – інтраректальне введення 0,9 % фізіологічного розчину; друга контрольна група – введення 50 % розчину етанолу; експериментальна група – введення DNBS у 50 % розчині етанолу) проведено визначення вмісту простаноїдів та циклооксигеназ у тканині товстої кишки імуноферментним методом.
Результати. Вміст PGE2 та PGI2 у тканині товстої кишки щурів дослідної групи був статистично достовірно вищим порівняно з 1-ю та 2-ю контрольними групами. Вміст ПГЕ2 також був підвищений у 2-й контрольній порівняно з 1-ю контрольною групою. Збільшення PGI2 у 2-й контрольній групі порівняно з 1-ю контрольною групою не було значущим. Вміст TBX2 та PGF2α в дослідній та 2-й контрольній групах був достовірно нижчим порівняно з 1-м контролем. Рівень 8-ізо-PGF2α (простаноїду неферментативного походження) у щурів експериментальної групи був значно вищим порівняно з обома контрольними. Вміст 8-ізо-PGF2α у 2-й контрольній групі був значно вищим порівняно з 1-ю. Вміст обох ізоформ ЦОГ у тканині товстої кишки щурів дослідної та 2-ї контрольної груп був достовірно нижчим порівняно з 1-ю контрольною групою.
Висновки. Обидві ізоформи ЦОГ експресуються в товстій кишці контрольної групи, що вказує на участь ЦОГ-2 у підтримці фізіологічних функцій тканини товстої кишки за нормальних умов. Всі досліджувані зміни показників, крім PGI2, зумовлені етанолом, а не DNBS. І 50 % етанол, і DNBS у 50 % етанолі стимулюють перекисне окислення ліпідів, що підтверджено значним збільшенням вмісту 8-ізо-PGF2α. Зміни вмісту PGE2 та PGF2α на тлі зниження рівнів ЦОГ-1 та ЦОГ-2 при експериментальному виразковому коліті, швидше за все, є адаптивною реакцією, спрямованою на підтримку гомеостазу товстої кишки. Зміни вмісту PGI2 викликані DNBS, а не етанолом.

Ключові слова: **простаноїди, циклооксигеназа, виразковий коліт, щури**