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N. V. Denysenko, O. Ya. Sklyarov
DANYLO HALYTSKYI LVIV NATIONAL MEDICAL UNIVERSITY

THE ACTION OF COX/LOX INHIBITORS ON ANTIOXIDANT SYSTEM AND MORPHOLOGICAL STATE OF RAT'S COLON MUCOSA UNDER THE CONDITIONS OF STRESS

Introduction. *Extensive, and often uncontrolled, use of cyclooxygenase (COX) inhibitors, as well as the psychological stress, are important factors of inflammatory diseases development in the digestive tract, including the large intestine. The activation of lipoperoxidation processes is one of the pathogenetic links of the development of ulcers, which can serve as a marker for both the intensity of inflammation and the onset of proinflammatory state.*

The aim of the study *– to find out the influence of certain COX and lipoxygenase (LOX) inhibitors on the activity of free radical oxidation and the morphological state of the colon mucosa (CM) under the conditions of their independent action and under the conditions of stress.*

Research Methods. *A model of 5 hours water-immobilization stress was selected for the stress simulation, for inhibition of COX and LOX – naproxen, celecoxib and compound 2A5DHT, which were administered intragastrically, in a single dose of 10 mg/kg. The morphological study of CM and the determination of the antioxidant enzymes activity in the CM homogenates were conducted.*

Results and Discussion. *The single action of naproxen caused increase of SOD, catalase, MPO activity and TBA-active products concentration in the CM. Similar changes were noted under the conditions of stress. Administration of naproxen under the conditions of stress caused the increase of SOD activity compared to WIS action and increase of TBA-active products concentration, activity of catalase and MPO compared to naproxen action.*

Conclusions. *It was found that non-selective COX inhibition was accompanied by proinflammatory effect in the CM, likely based on the prooxidant action of the nonselective COX inhibitor, which was confirmed by the activation of SOD. Selective COX-2 inhibition and inhibition of COX-2/5-LOX showed an anti-inflammatory effect due to a more effective mechanism of action.*

KEY WORDS: **cyclooxygenase; lipoxygenase; stress; antioxidant defense; free radical oxidation; colon.**

INTRODUCTION. The COX inhibitors are widely used in medicine as non-steroidal anti-inflammatory drugs (NSAIDs) due to their ability to block the synthesis of proinflammatory prostaglandins (PGs) [1]. As many of them, mainly analgesics, belong to over-the-counter medicines group, it has resulted in the uncontrolled use of NSAIDs [2].

The inhibition of COX results also in the decrease of gastroprotective PGs production, which leads to the insufficient production of mucus and bicarbonates by the digestive tract organs mucosa [3]. Therefore, ulcers development of the digestive tract mucosa is the most common side effect of NSAIDs [4]. The research of safer, but enough effective NSAIDs is an actual question of different sciences related to the medicine [5]. Modern directions of NSAIDs improvement include the synthesis of more selective COX-2 inhibitors [1], dual inhibitors of COX-2 and 5-LOX [6] and incorporation of different radicals with cytoprotective properties into the known molecule structure [7].

The psychological stress is another trigger of inflammatory diseases of the digestive tract development, as stress is accompanied by increased production of catecholamines and cortisol later [8]. The action of adrenaline on the colon mucosa (CM) manifests by vasoconstriction [9] and disturbed motor function [10]. Cortisol and other corticosteroids, like corticoliberin and urocortin, cause ischemia, increased cell membrane permeability, visceral sensitivity [11] on the one hand and inhibit phospholipase A_2 via lipocortin synthesis induction [12] on the other. Taken together, these mechanisms can activate cell damage, and result in the free radical oxidation activation.

Free radicals (superoxide radical, hydrogen peroxide, hydroxyl radical etc.) are produced by the CM in response to the action of infectious factors under the normal conditions and provide cell death

under the pathological states like inflammation, stress, the action of chemical or physical stimuli [13]. Lipids of cell and mitochondrial membranes are the most sensitive molecules to free radical oxidation [14]. The final product of their chemical transformation is malonic dialdehyde, which can bind with thiobarbituric acid (TBA) [15]. The contraction to the lipid peroxidation is provided by the antioxidant enzymes – superoxide dismutase (SOD), catalase, glutathione peroxidase [16] and in some way by myeloperoxidase (MPO), which transforms hydrogen peroxide by neutrophils, and is also a marker of neutrophil infiltration [17].

The aim of the study – to find out the influence of certain COX and LOX inhibitors on the activity of lipid peroxidation and the morphological state of the CM under the conditions of their independent action and under conditions of stress.

RESEARCH METHODS. The experiment was conducted on 80 outbred rats of both sexes with the body weight of 200–240 g. All manipulations with the animals were carried out according to European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes and permitted by Bioethics Committee of Danylo Halytskyi Lviv National Medical University (Protocol No. 3, 16.03.2015). The animals were kept on the standard diet with free access to the water.

The rats were divided into 8 groups: group 1 was a control group (intact), animals of the groups 2, 3 and 4 were administered COX inhibitors – nonselective naproxen (group 2), COX-2 selective celecoxib (group 3) and dual COX-2/5-LOX 2A5DHT (group 4). All the COX inhibitors were administered intragastrically at a single dose of 10 mg/kg. The animals of the groups 5–8 were fasting for 24 hours and then were subjected to water-immersion stress (WIS) duration of 5 hours, water temperature was 20–23 °C [18]. The rats of the groups 6–8 were administered COX inhibitors 1 hour before WIS by the same scheme as animals of groups 2–4. Euthanasia was carried out by the urethan injection at a dose of 4 g/kg.

The colons were washed with the saline solution, the samples were taken for the histological examination and average goblet cells number in a crypt was measured using ImageJ program. The CM was removed and the homogenates were prepared in the 0.9 % saline solution (1:5). The activity of SOD [19], catalase [20], MPO [21] and the concentration of TBA-active products [22] was measured in the CM homogenates.

Statistical analysis was performed using program OriginPro 7.0. Data are presented as the mean and standard deviation. The reliability was determined using the Student`s test because distribution, determined using the Shapiro-Wilk test, was normal.

RESULTS AND DISCUSSION. The action of COX inhibitors did not cause any morphological changes in the CM. The administration of naproxen caused increase of TBA-active products concentration by 16 % ($p<0.05$), activity of SOD by 37 % ($p<0.05$), catalase by 37 % ($p<0.01$) and MPO by 50 % ($p<0.01$) compared to the control group (Table 1). Absence of morphological changes and increase in TBA-active products concentration in CM under the action of naproxen was also noted in our previous investigation [23]. There were no significant changes in studied biochemical indices in groups of celecoxib and 2A5DHT compared to control group.

We suppose that the activation of free radical oxidation may be caused by two reasons. First – by special properties of naproxen, which can increase expression of NADPH-oxidase-4 [24] thus causing the increased concentration of superoxide radical and activation of SOD, which turns superoxide into hydrogen peroxide. The increased concentration of hydrogen peroxide leads to the increased activity of catalase and MPO, which are using it as a substrate. The increased concentration of both superoxide radical and hydrogen peroxide activates lipid peroxidation, so it results in increased TBA-active products concentration. Another possible reason is connected with the mechanism of naproxen action – it inhibits the synthesis of protective PGs [4],

Table 1 – **The concentration of TBA-active products and activity of SOD, catalase and MPO in CM under the action of COX-inhibitors (M±m)**

Group	TBA-active products, μmoles/g tissue	SOD, μmoles of nitroblue tetrazolium/min·mg of protein	Catalase, μmoles of H_2O_2/ min·mg of protein	MPO, μmoles of H_2O_2/ min·mg of protein
Control (n=10)	0.95±0.10	7.31±1.43	15.80±2.30	0.04±0.01
Naproxen (n=10)	1.10±0.05*	9.99±1.36*	21.60±2.65**	0.06±0.01**
Celecoxib (n=10)	0.95±0.16	7.47±1.69	15.50±2.89	0.05±0.01
2A5DHT (n=10)	1.04±0.17	6.18±1.25	17.60±3.27	0.05±0.01

Notes. * – $p<0.05$ compared to control group; ** – $p<0.01$ compared to control group.

so CM is not protected enough from aggressive factors present in the feces.

Combined action of WIS and COX inhibitors did not predetermine any macroscopic changes of CM, but we found out that the CM surface was damaged and there were changes in histological indices. In particular, there were CM erosions under conditions of WIS, combined action of naproxen and WIS caused increase of erosions, whereas action of celecoxib and 2A5DHT under conditions of WIS contributed to the preservation of CM integrity (Fig. 1, erosions are marked with arrows). Similar histological changes were noted under the action of WIS and combined action of naproxen and WIS in rat's gastric mucosa [25].

The investigation of histological specimens revealed that under conditions of WIS the average number of goblet cells in crypt decreases by 44 % ($p<0.001$) compared to control group (Fig. 2). The administration of naproxen and celecoxib under conditions of WIS did not change it reliably compared to WIS group, whereas 2A5DHT caused increase of average goblet cells number by 30 % ($p<0.05$) compared to WIS group. Goblet cells are producing and accumulate mucus, so the increase or decrease of their number reflects the level of the CM protection. These data indicate that 2A5DHT has more effective anti-inflammatory effect and is less ulcerogenic due to its mechanism of action, which provides synthesis of protective PGs and inhibit production of both inflammatory PGs and leucotriens.

The action of WIS caused increase in TBA-active products concentration by 57 % ($p<0.001$), activity of SOD by 44 % ($p<0.001$), catalase – by 43 % ($p<0.001$), MPO – by 325 % ($p<0.001$) compared to control group (Table 2). We received increased concentration of TBA-active products in the CM [26] and MPO activity in gastric mucosa [25] and under conditions of WIS previously. Activation of the antioxidant enzymes is a marker of free radicals accumulation, which is possibly connected with ischemia, developed under the action of adrenaline. The administration of naproxen under

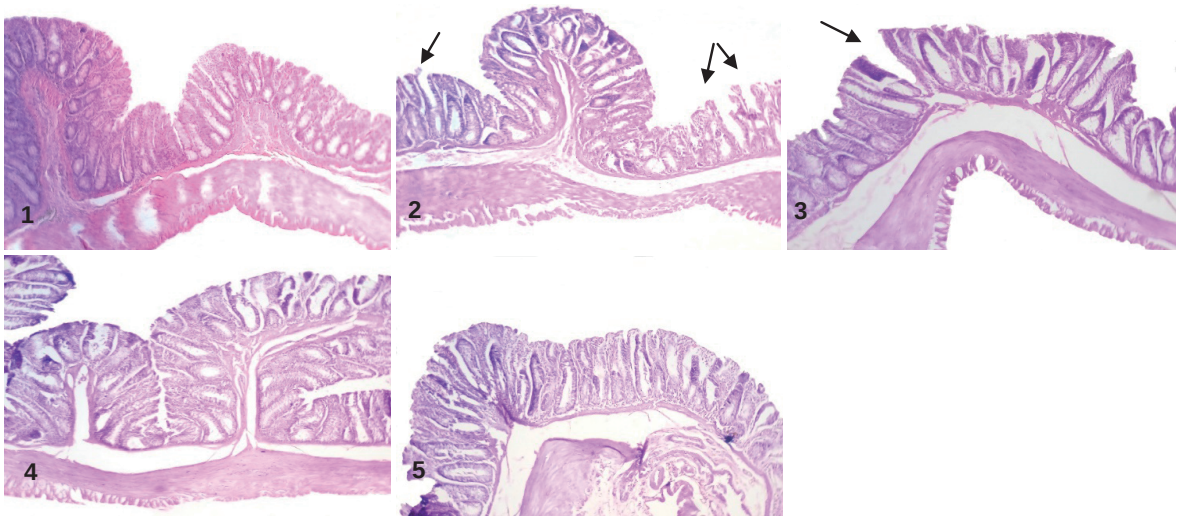

Fig. 1. Colon histology, hematoxylin-eosin stained, ×100 magnification.
Notes. 1 – control group; 2 – WIS group; 3 – WIS + naproxen group; 4 – WIS + celecoxib group; 5 – WIS + 2A5DHT group.

Table 2 – **The concentration of TBA-active products and activity of SOD, catalase and MPO in CM under the combined action of WIS and COX-inhibitors (M±m)**

Groups	TBA-active products, μmoles/g tissue	SOD, μmoles of nitroblue tetrazolium/min·mg of protein	Catalase, μmoles of H_2O_2/ min·mg of protein	MPO, μmoles of H_2O_2/ min·mg of protein
Control (n=10)	0.95±0,10	7.31±1.43	15.80±2.30	0.04±0.01
WIS (n=10)	1.49±0.19***	10.50±1.37***	22.60±2.71***	0.13±0.02***
WIS+naproxen (n=10)	1.36±0.15^^	13.40±1.54#	26.10±2.67^^	0.15±0.03^^^
WIS+celecoxib (n=10)	1.39±0.13	11.00±1.60	23.50±2.44	0.14±0.03
WIS+2A5DHT (n=10)	1.39±0.18	9.77±1.11	22.00±2.11	0.12±0.03

Notes:
1. *** – $p<0.001$ compared to control group.
2. # – $p<0.05$ compared to WIS group.
3. ^^ – $p<0.01$ compared to naproxen group.
4. ^^^ – $p<0.001$ compared to naproxen group.

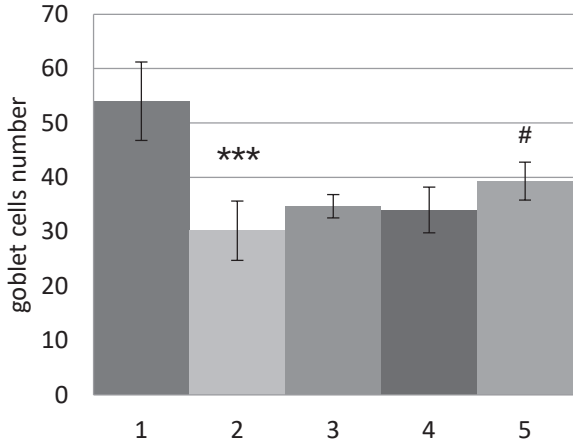

Fig. 2. The average number of goblet cells in crypt.

Notes. 1 – control group; 2 – WIS group; 3 – WIS + naproxen group; 4 – WIS + celecoxib group; 5 – WIS + 2A5DHT group; *** – $p<0.001$ compared to control group; # – $p<0.05$ compared to WIS group.

the conditions of WIS promoted increase of SOD activity by 28 % ($p<0.05$) compared to WIS group; increase of TBA-active products concentration by 24 % ($p<0.01$), activity of catalase by 21 % ($p<0.01$), MPO – by 250 % ($p<0.001$) compared to naproxen group (Table 2). We did not note increase of TBA-active products in any of groups compared to WIS group, the same results we received in previous experiment, but there was the decrease of TBA-active products compared to WIS group in gastric mucosa [26]. Probably, upper gastro-intestinal tract is more sensitive to WIS and NSAIDs action compared to colon. Interestingly, that increase of SOD and catalase activity under the action of naproxen is almost the same as under the WIS action. These data indicate the prooxidative action of naproxen, which increases under conditions of stress and probably is connected with NADPH-oxidase expression activation [24]. Another mechanism may be connected with protective PGs synthesis inhibition by both naproxen via COX-1 [3] and cortisol via lipocortin [12], so it results in decrease of mucosal layer protective function. Administration of celecoxib and 2A5DHT did not cause reliable pro- or antioxidant action on CM under the conditions of WIS, which confirms that WIS action is more determinative.

CONCLUSIONS. 1. Non-selective COX inhibitor (naproxen) has a prooxidant and proinflammatory action on colon mucosa, which is very similar to the action of stress and manifested by increase of TBA-active products concentration and activity of SOD, catalase, MPO.

2. Combined action of stress and non-selective COX inhibitor ameliorates free radical oxidation, which was proved by SOD activation.

3. Selective COX-2 and dual COX-2/5-LOX inhibitors (celecoxib and 2A5DHT) did not promote proinflammatory or prooxidant action on colon mucosa neither under conditions of their action alone, nor under the conditions of stress.

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Н. В. Денисенко, О. Я. Скляров
ЛЬВІВСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ ДАНИЛА ГАЛИЦЬКОГО

ВПЛИВ ІНГІБІТОРІВ ЦИКЛООКСИГЕНАЗИ/ЛІПООКСИГЕНАЗИ НА АНТИОКСИДАНТНУ СИСТЕМУ ТА МОРФОЛОГІЧНИЙ СТАН СЛИЗОВОЇ ОБОЛОНКИ ТОВСТОЇ КИШКИ ЩУРІВ ЗА УМОВ СТРЕСУ

Резюме

Вступ. *Широке і часто неконтрольоване застосування інгібіторів циклооксигенази, а також психологічний стрес – важливі фактори виникнення хронічних запальних захворювань органів травлення, в тому числі й у товстій кишці. Однією з патогенетичних ланок утворення виразок є активація процесів ліпопероксидації, що може слугувати маркером як інтенсивності запалення, так і виникнення прозапального стану.*

Мета дослідження *– з'ясувати вплив деяких інгібіторів циклооксигенази та ліпооксигенази на активність вільнорадикального окиснення і морфологічний стан слизової оболонки товстої кишки за умов самостійної дії та на тлі стресу.*

Методи дослідження. *Для моделювання стресу було обрано модель водно-іммобілізаційного стресу тривалістю 5 год з метою інгібування циклооксигенази та ліпооксигенази – напроксен, целекоксиб і спо-*

луку 2A5DHT, які вводили внутрішньошлунково одноразово в дозі 10 мг/кг. Виконували морфологічне дослідження слизової оболонки товстої кишки і визначали активність ензимів антиоксидантного захисту в гомогенатах слизової оболонки товстої кишки.

Результати й обговорення. *Самостійна дія напроксену зумовила зростання активності супероксиддисмутази, каталази, мієлопероксидази та концентрації ТБК-активних продуктів у слизовій оболонці товстої кишки. Схожі зміни було відзначено за умов водно-іммобілізаційного стресу. Введення напроксену на тлі водно-іммобілізаційного стресу спричинило підвищення активності супероксиддисмутази порівняно з дією цього стресу, збільшення вмісту ТБК-активних продуктів, зростання активності каталази і мієлопероксидази порівняно з дією напроксену.*

Висновки. *Встановлено, що неселективне інгібування циклооксигенази супроводжується прозапальним впливом на слизову оболонку товстої кишки, в основі якого, ймовірно, лежить прооксидантна дія неселективного інгібітора циклооксигенази, що підтверджується активацією супероксиддисмутази. Селективне інгібування циклооксигенази-2 та інгібування циклооксигенази-2 і 5-ліпооксигенази проявляють протизапальну дію за рахунок більш ефективного механізму дії.*

КЛЮЧОВІ СЛОВА: **циклооксигеназа; ліпооксигеназа; стрес; антиоксидантний захист; вільнорадикальне окиснення; товста кишка.**

Н. В. Денисенко, А. Я. Скляров
ЛЬВОВСКИЙ НАЦИОНАЛЬНЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ ИМЕНИ ДАНИЛА ГАЛИЦКОГО

ВЛИЯНИЕ ИНГИБИТОРОВ ЦИКЛООКСИГЕНАЗЫ/ЛИПООКСИГЕНАЗЫ НА АНТИОКСИДАНТНУЮ СИСТЕМУ И МОРФОЛОГИЧЕСКОЕ СОСТОЯНИЕ СЛИЗИСТОЙ ОБОЛОЧКИ ТОЛСТОЙ КИШКИ КРЫС В УСЛОВИЯХ СТРЕССА

Резюме

Вступление. *Широкое и часто неконтролируемое применение ингибиторов циклооксигеназы, а также психологический стресс – важные факторы возникновения хронических воспалительных болезней органов пищеварения, в том числе и в толстой кишке. Одним из патогенетических звеньев образования язв является активация процессов липопероксидации, что может служить маркером как интенсивности воспаления, так и возникновения провоспалительного состояния.*

Цель исследования *– определить влияние некоторых ингибиторов циклооксигеназы и липооксигеназы на активность свободнорадикального окисления и морфологическое состояние слизистой оболочки толстой кишки в условиях самостоятельного действия и на фоне стресса.*

Методы исследования. *Для моделирования стресса было выбрано модель водно-иммобилизационного стресса продолжительностью 5 ч с целью ингибирования циклооксигеназы и липооксигеназы – напроксен, целекоксиб и соединение 2A5DHT, которые вводили внутрижелудочно однократно в дозе 10 мг/кг. Выполняли морфологическое исследование слизистой оболочки толстой кишки и определяли активность энзимов антиоксидантной защиты в гомогенатах слизистой оболочки толстой кишки.*

Результаты и обсуждение. *Самостоятельное действие напроксена обусловило возрастание активности супероксиддисмутазы, каталазы, миелопероксидазы и концентрации ТБК-активных продуктов в слизистой оболочке толстой кишки. Похожие изменения были отмечены в условиях водно-иммобилизационного стресса. Введение напроксена на фоне водно-иммобилизационного стресса вызвало повышение активности супероксиддисмутазы в сравнении с этим стрессом, увеличение содержания ТБК-активных продуктов, возрастание активности каталазы и миелопероксидазы в сравнении с действием напроксена.*

Выводы. *Установлено, что неселективное ингибирование циклооксигеназы сопровождается провоспалительным влиянием на слизистую оболочку толстой кишки, в основе которого, вероятно, лежит прооксидантное действие неселективного ингибитора циклооксигеназы, подтверждающееся активацией супероксиддисмутазы. Селективное ингибирование циклооксигеназы-2 и ингибирование циклооксигеназы-2 и 5-липооксигеназы проявляют противовоспалительное действие за счет более эффективного механизма действия.*

КЛЮЧЕВЫЕ СЛОВА: **циклооксигеназа; липооксигеназа; стресс; антиоксидантная защита; свободнорадикальное окисление; толстая кишка.**

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Address for correspondence: *N. V. Denysenko, Danylo Halytskyi Lviv National Medical University, Pekarska street, 69, Lviv, 79010, e-mail: denysenko.natalka@gmail.com.*