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### ИЗМЕНЕНИЯ БЕЛКОВОГО СОСТАВА СЫРОВАТКИ КРОВИ И ГОМОГЕНАТА ПИЩЕВОДА ПРИ РАЗВИТИИ КИСЛОТНОГО ОЖОГА ПИЩЕВОДА НЕПОЛОВОЗРЕЛЫХ КРЫС

За последние десятилетия отмечается стабильное увеличение числа химических ожогов пищевода. В детском возрасте кислотные ожоги пищевода чаще всего встречаются в возрасте от 1 года до 8 лет. В месте локализации химической травмы увеличиваются процессы синтеза и деградации белков. Рубцовые изменения пищевода, развивающиеся в результате ожога, остаются одной из наиболее сложных проблем. Несмотря на многочисленные исследования, недостаточно изучены вопросы заживления и процессов рубцевания на клеточном и молекулярном уровне. Показаны количественные изменения белкового состава в условиях развития кислотного ожога пищевода. Дальнейшее исследование процессов заживления может быть полезным в создании эффективных подходов для профилактики образования рубцовых изменений пищевода.

Ключевые слова: ожог пищевода, белковые фракции, электрофорез.

UDK 616.34-002-02-092+616.833

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### THE ROLE OF CENTRAL AND PERIPHERAL D2R RECEPTORS IN THE MECHANISM OF COLONIC VASCULAR PERMEABILITY DURING EXPERIMENTAL COLITIS IN RATS

We investigated the involvement of central and peripheral D2 dopaminergic receptors in the mechanism of vascular permeability in rat's colon during experimental ulcerative colitis. Ulcerative colitis was induced in male white inbred rats by 6 % iodoacetamide enema. For the investigation of central and peripheral D2R, separate and joint injections of D2R antagonist domperidone (2 mg/100 g, per os) and D2R agonist quinpirole (1 mg/100 g, per os) were applied. Central D2R were destroyed by neurotoxin injection – 6-OHDA. Colonic vascular permeability was measured by colonic extravasation of 1,5 % Evans blue. It was observed that blockade of peripheral D2R decreased colonic vascular permeability, while simultaneous activation of central D2R and inhibition of peripheral D2R have additive positive effect in prevention of increased colonic vascular permeability during experimental colitis.

Key words: D2 dopamine receptors, vascular permeability, ulcerative colitis.

**Introduction.** Inflammatory bowel diseases (IBD) development in human, as well as in animal models, is usually supported by increase of vascular permeability, which leads to the tissue edema. Number of mediators such as angiotenin, chemokines (IL-8, IL-10), coagulation factors, cytokines (IFN- $\gamma$ , IL-13) and growth factors, mainly vascular endothelial growth factor (VEGF), affect vascular permeability and angiogenic balance. Endothelial cells produce proinflammatory mediators in response to the activation of immune cells and changes in tissue microenvironment. Many of the cytokines, deregulated during IBD pathogenesis, are pro-angiogenic: e.g., IL-17, which is synthesized by invasive Th17 cells and TNF $\alpha$ , which is synthesized by macrophages, monocytes and endothelial cells [1].

It should be mentioned that endothelium of colonic blood vessels is more permeable than vascular endothelium in brain and less penetrative comparing to the endothelium of liver and spleen blood vessels, which is related to the different amount of connections between the cells of endothelium [2]. Three different types of vascular permeability were previously defined: basal vascular permeability of normal tissues, acute vascular hyperpermeability, chronic hyperpermeability, which is typical for pathological angiogenesis. While basal permeability is most typical for capillaries because of their structure, acute vascular hyperpermeability appears in postcapillary venules in response to single or short-term influence of VEGF, histamine, serotonin etc. Most of them are present in tissue mast cells under normal conditions and may be released under the influence of mast cell degranulation factors. The increase in permeability in this case is performed through the contraction of endothelial cells, which leads to the 'channel' appearance between them. Under the constant influence of permeability-increasing factors, deep changes in venules structure and functioning appear, which lead to the chronic hyperpermeability and pathologic angiogenesis [3].

Dopamine is a neurotransmitter, which is responsible for the happiness state and acts through two classes of

dopamine receptors – D1 class, which consist of D1 and D5 subtypes and D2 class, which consists of D2, D3 and D4 subtypes. Expression of D1, D2, D3 and D5 dopamine receptors was found in mucosal layer of upper (stomach) and lower (small intestine and colon) parts of the gastrointestinal tract.

There is direct and indirect evidence that disruption of dopaminergic system might have an influence in IBD pathogenesis. We showed that patients with schizophrenia, which is characterized by hyperdopaminergic activity, have less susceptibility to IBD development [4]. Meanwhile during Parkinson's disease, which is characterized by destroyed dopaminergic neurons in central nervous, the increased risk of IBD development was observed [5]. Previously we determined changes in D2R expression in colon mucosa of patients with IBD and experimental colitis [6]. D2R activation facilitated healing of experimental colitis lesions via decreasing of endothelial permeability and, as a result, reduction of colonic inflammation [7].

The aim of this work to determine whether central or peripheral D2 dopamine receptors affect vascular permeability in rat's colon during experimental UC.

**Materials and methods. Animals.** Male white inbred rats (170-200 g, n=25) were housed under standard vivarium conditions. All animals had unlimited access to tap water and Purina chow. These studies were approved by Bioethical Committee of 'Institute of Biology and Medicine', Taras Shevchenko National University of Kyiv (Kyiv, Ukraine), protocol №1 from 20.02.2017.

**Iodoacetamide-Induced Colitis Model.** Experimental UC in rats was induced by 6 % IA injection. IA is a widely used SH-alkylator [8]. This model of chemically induced UC is advantageous due to sufficient colonic lesions induction; during first 1-2 hours after IA enema such parameters as increased vascular permeability, massive mucosal edema etc can be seen with further erosions and ulcer formation (6-12 h) and acute and chronic inflammation (7-14 d). In brief, 0.1 ml of 6 % IA (Sigma, USA) dissolved in 1 % methylcellulose (Sigma, USA) or 0.1 ml of 1 % methylcellulose (MC) was given through rubber catheter

(Nelaton S-8, Rusch, Germany) 7 cm from anus. Rats were subjected to autopsy 1 h after intracolonic IA administration.

**Vascular permeability assay.** For the quantitative measurement of colonic vascular permeability Evans blue assay was applied [9]. Evans blue irreversibly binds to albumin and crosses endothelial barrier in form of albumin/Evans blue conjugate ( $M_w \approx 67$  kDa). Rats were anesthetized with urethane. Evans blue (1,5 %) in dose of 100  $\mu$ l/100 mg was injected intravenously 30 min before autopsy, which was performed 60 min after 6 % IA enema or vehicle (1 % MC). At autopsy 7 cm of colon were removed, rinsed in saline, gently blotted with filter paper and weighed. Using metal spatula the mucosa was gently scraped from the mucosal layer. Evans blue was extracted from the tissue using formamide and measured by spectrophotometry at 612 nm. Results were expressed as mg of dye/g colon wet weight.

**Destruction of central dopaminergic neurons.** Chronic unilateral dopamine deficiency was performed by disruption of dopaminergic neurons of substantia nigra by stereotaxic microinjections of 12  $\mu$ g of selective neurotoxin 6-hydroxydopamine (6-OHDA) (Sigma, USA) as described [10]. Briefly, under the nembutale anesthesia (50 mg/kg, i.p., Sigma, USA) rats were put into the modified stereotax (SEG-4). Then animals were scalped and trepanated by injection needle in the area 2,2 mm in caudal direction and 1,5 mm in lateral direction from bregma. After that animals were given pargilin (40 mg/kg, i.p., Sigma, USA) to inhibit metabolic conversion of 6-OHDA by monoaminooxidase and desipramine (25 mg/kg, i.p., Sigma, USA) to block neurotoxin capture by noradrenergic cells. 4  $\mu$ l of 6-OHDA (12  $\mu$ g) were inserted into the brain into the bur hole in 2,8 mm depth from cranium with the speed of 1  $\mu$ l per minute (every 15 s). One week after the administration of 6-OHDA the number of destroyed central dopaminergic neurons was estimated by apomorphine test. The intensity of movements was recorded for 30 min after apomorphine injection (0,5 mg/kg, i.p., Sigma, USA). Less than 180 turns per 30 min corresponded to 44 % of destroyed dopaminergic neurons of left hemisphere; more than 180 turns per 30 min – 95 % of destroyed dopaminergic neurons.

**Experimental design.** 1) To check the role of central and peripheral D2R in mechanisms of colonic vascular permeability. The selective D2R agonist quinpirole was gavaged in dose 1 mg/100 g (Sigma, USA, cat #85798089) *per os* 15 min before IA enema (75 min before autopsy). Quinpirole was dissolved in saline strictly before using. The peripheral D2R antagonist domperidone (Domrid, 'Cusum Pharm') was gavaged in dose 2 mg/100 g body weight *per os* 30 min before IA enema (90 min before autopsy). Quinpirole and domperidone were gavaged separately or consecutively. Saline (1 ml/rat) was gavaged as the vehicle. 2) To check the role of central dopaminergic system in mechanisms of colonic vascular permeability. 6-OHDA-treated or sham-lesioned rats were enrolled in experiment in 1 month after surgery. Rats were divided into 4 groups: I – sham-lesioned rats treated with MC (n=3); II 6-OHDA-lesioned rats treated with methylcellulose (MC) (n=3); III sham-lesioned rats treated with IA (n=3); IV – 6-OHDA-lesioned rats treated with IA (n=3). Colonic vascular permeability in rats was assessed in 60 min after IA or MC enema.

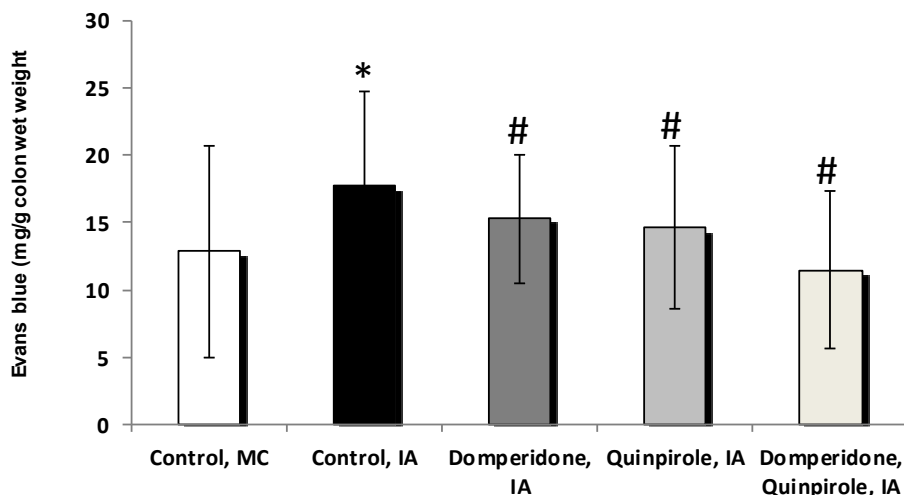
**Statistical analysis.** Quantitative results were expressed as mean  $\pm$ SD. Statistical significance was determined by Student's t-test, and p-values of <0.05 were considered statistically significant.

**Results and discussion.** It is well known that increased vascular permeability is a major contributor to acute inflammatory response development and perpetuation of chronic inflammation. In our study rats injected with 6 % IA had increased vascular permeability in 37.6 % (p<0.05) vs. control group (MC) (Fig. 1). These results are in line with previous data on increased vascular permeability during experimental UC [7].

On the models of ovarian hyperstimulation syndrome performed on human luteinized granulosa cells *in vitro* and *in vivo*, commercially available D2R agonist cabergoline showed effectiveness in prevention of increased vascular permeability by inhibition of VEGF protein production and secretion. Moreover, cabergoline in small doses activated D2R and reduced VEGF-mediated vascular permeability without affecting angiogenesis [11; 12]. Also the effectiveness of the D2R agonists was shown for treatment of lung cancer, which was performed on a LLC1 murine lung cancer model. Tumour angiogenesis was inhibited by D2R agonist via abrogation VEGFR-2-mediated signalling in endothelial cells [13].

For the determination of D2R role in colonic vascular permeability during experimental UC, rats were treated with D2R agonist quinpirole. Quinpirole decreased 23.9 % (p<0.05) colonic vascular permeability in rats with IA-induced UC (Fig. 1). So, activation of D2R decreased vascular permeability in rats with experimental UC and could indicate about the protective role of D2R. These data support previous research about the protective role of D2R in IBD pathogenesis [7]. Previous study showed that both central and peripheral dopamine plays a mechanistic role in duodenal ulceration [14; 15]. Quinpirole is a D2R agonist, which is able to cross blood-brain barrier and affects both central and peripheral dopaminergic neurons. Because of that question about the positive influence of central or peripheral D2R still remains open.

To distinguish the role of central and peripheral D2R in regulation of colonic vascular permeability, selective D2R antagonist domperidone was used in our study. Domperidone does not cross blood-brain barrier and has an influence only on peripheral dopamine receptors [16]. Domperidone is commercially available antagonist and is used for treatment of gastroparesis, functional dyspepsia, nausea and vomiting and pediatric reflux [17; 18; 19; 20]. Pre-treatment with domperidone decreased in 18.8 % (p<0.05) colonic vascular permeability in rats with IA-induced UC vs. saline-treated rats (Fig. 1). To our best knowledge, these data are the first indication that activation of peripheral dopaminergic neurons might play the negative role in the IBD pathogenesis via increase colonic vascular permeability. Previously, beneficial effects of D2R antagonists were shown in peptic ulcer disease. Namely, risperidone, D2R and 5-HT(2A) receptor antagonist pre-treatment reversed the stress-induced alteration in hexosamine, PGE(2) and microvascular permeability [21]. Another antipsychotic D2R antagonist aripiprazole showed significant antiulcer and gastroprotective activity on the model of ethanol induced gastric ulcers [22].

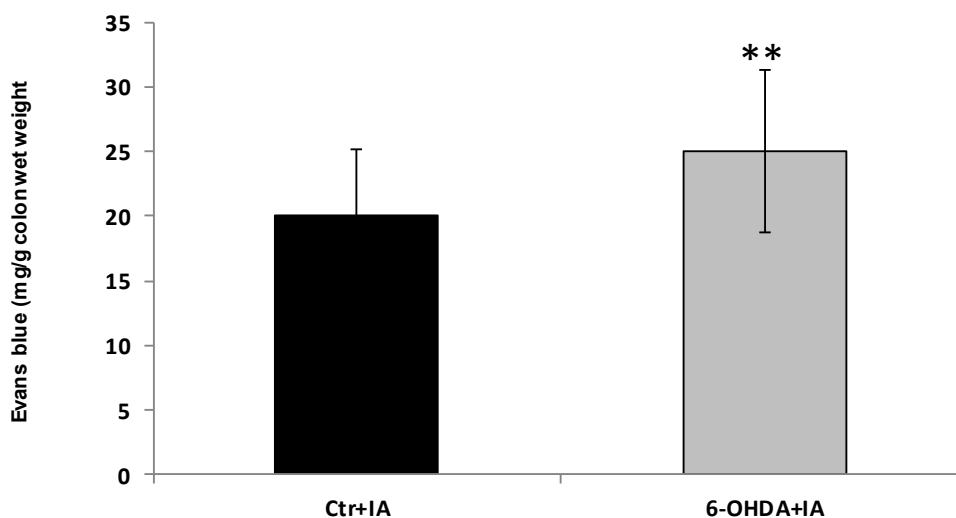


**Fig. 1. The effect of peripheral D2R antagonist domperidone (D), D2R agonist quinpirole (Q) and their combination on colonic vascular permeability during the IA-induced UC in rats.**  
M $\pm$ SD, \* – p<0.05, vs. control group, treated with MC; # – p<0.05, vs. IA group

Meanwhile, under the joint administration of quinpirole and domperidone level of colonic vascular permeability during IA-induced UC was decreased by 48.2 % (p<0.05), that almost twice lower than after single administration either quinpirole or domperidone (Fig. 1). The received results might indicate about the positive influence of central branch of dopaminergic system in IBD development and progression. Till date, there is no direct evidence on the central dopamine role in IBD development and progression, except evidence that patients with Parkinson's

disease had increased levels of pro-inflammatory cytokines and intestinal permeability, which are key features of IBD pathogenesis [23; 24].

To confirm the hypothesis on the beneficial effect of central dopaminergic system in the prevention of increased vascular permeability, we measured the level of colonic vascular permeability in rats with chemically destroyed central dopaminergic neurons during experimental UC (Fig. 2).



**Fig. 2. Colonic vascular permeability in the rats with damaged central dopaminergic neurons during IA-induced UC. Results were expressed as M $\pm$ SD; n=3 rats/group. \*\*p<0.01;**

We found that colonic vascular permeability was increased 40.0 % (p<0.01) in rats with destroyed dopaminergic neurons vs. sham-lesioned rats with IA-induced UC.

**Conclusions.** We showed for the first time that blockade of peripheral D2R decrease the colonic vascular permeability, while simultaneous activation of central D2R and inhibition of peripheral D2R have additive positive

effect in prevention of increased colonic vascular permeability during experimental colitis.

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Submitted on 13.03.17

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### РОЛЬ ЦЕНТРАЛЬНИХ І ПЕРИФЕРИЧНИХ D2 РЕЦЕПТОРІВ У МЕХАНІЗМІ ЕНДОТЕЛІАЛЬНОЇ ПРОНИКНОСТІ ТОВСТОЇ КИШКИ ЩУРІВ ЗА УМОВ ЕКСПЕРИМЕНТАЛЬНОГО КОЛІТУ

Визначено залучення центральних і периферичних D2 дофамінергічних рецепторів у механізм ендотеліальної проникності товстої кишки щурів з експериментальним виразковим колітом (ВК). ВК викликали у білих нелінійних щурів-самців шляхом ректального введення 6 % йодоацетаміду. Для дослідження ролі центральних і периферичних D2P щурам окремо та сумісно вводили антагоніст D2P домперидон (2 мг/100 г, per os) та агоніст D2P квінпірол (1 мг/100 г, per os). Центральні дофамінергічні нейрони у щурів руйнували шляхом введення нейротоксину 6-OHDA. Ендотеліальну проникність товстої кишки щурів вимірювали за ступенем екстравазації 1.5 % фарби Еванса. Встановлено, що блокування периферичних D2P знижувало ендотеліальну проникність товстої кишки щурів, водночас активація центральних D2P та інгібування периферичних D2P мало додатковий позитивний ефект по запобіганню підвищеної ендотеліальної проникності товстої кишки щурів за експериментального ВК.

Ключові слова: D2 дофамінові рецептори, ендотеліальна проникність, виразковий коліт.

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### РОЛЬ ЦЕНТРАЛЬНЫХ И ПЕРИФЕРИЧЕСКИХ D2 РЕЦЕПТОРОВ В МЕХАНИЗМЕ ЭНДОТЕЛИАЛЬНОЙ ПРОНИЦАЕМОСТИ ТОЛСТОГО КИШЕЧНИКА КРЫС С ЭКСПЕРИМЕНТАЛЬНЫМ КОЛИТОМ

Определили вовлеченность центральных и периферических D2 дофаминергических рецепторов в механизм эндотелиальной проницаемости толстого кишечника крыс с экспериментальным язвенным колитом (ЯК). ЯК у белых нелинейных крыс-самцов вызывали путем ректального введения 6 % йодоацетамиды. Для исследования роли центральных и периферических D2P крысам отдельно и совместно вводили антагонист D2P домперидон (2 мг/100 г, per os) и агонист D2P квинпилол (1 мг/100 г, per os). Центральные дофаминергические нейроны у крыс разрушали путем введения нейротоксина 6-OHDA. Эндотелиальную проницаемость толстого кишечника крыс измеряли по степени экстравазации 1.5 % краску Эванса. Установлено, что блокирование периферических D2P снижало эндотелиальную проницаемость толстого кишечника крыс, в то время как активация центральных D2P и ингибирование периферических D2P имели дополнительный позитивный эффект на предотвращение повышенной эндотелиальной проницаемости толстого кишечника крыс при экспериментальном ЯК.

Ключевые слова: D2 дофаминовые рецепторы, эндотелиальная проницаемость, язвенный колит.

UDK 577.112

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### STATE OF HYPERGLYCEMIA ANIMALS IN THE CONSUMPTION OF HIGH-CALORIE DIET WITH THE BIONANOCOMPOSITE ADDITION

Glucose level and glucose tolerance test in blood of rats under conditions of obesity induced by consumption of high-calorie diet have been determined. It was also researched these indicators in the blood of animals that consumpt high-calorie diet with added bionanocomposite. These data suggest bionanocomposite preventive effect on the development of key indicators prediabetes.

Key words: glucose, glucose tolerance test, bionanocomposite, prevention, obesity.

**Introduction.** Obesity is a significant health problem worldwide and its incidence has more than doubled during the last 20 years [1]. Obesity is characterized by both a large increase in body weight and an increase in body fat exceeding standard measures. Obesity is a leading risk factor for the development of cardiovascular disease, and malignancies, and also has an impact on respiratory diseases such as asthma, chronic obstructive pulmonary disease as well as obesity hypoventilation syndrome and sleep apnea [2-4]. Obesity is associated with most of the components of metabolic syndrome, the leading cause of type 2 diabetes. The comorbidities of obesity and type 2 diabetes associated with hyperglycemia (high blood glucose and impaired glucose tolerance). Therefore determination of glucose and glucose tolerance test is an important in period of prevention or treatment obesity.

Features of metabolism at obesity can be the basis for the study of biologically active compounds of plant origin for the prevention of pathology. There is greater need to study the pharmacological and toxicological effects of herbal products to examine their clinical efficacy and safety. Because, every drug has potential side effects. They are not completely safe in this regard. Herbal supplements are being extensively used due to their

effectiveness in managing many chronic disorders. They are cost-effective, and exert less to no toxic side-effects in comparison with many chemically synthesized drugs [5].

Out of many such medicinal plants, fenugreek [*Trigonella foenum-graecum* Linn (Fabaceae)] has recently attracted the attention of scientists from across the globe. Fenugreek belongs to the family Fabaceae and is applied in many parts of the world for the treatment of diabetes. Fenugreek is well known for its antidiabetic properties [6-9]. The plant has been employed against different diseases including diabetes.

In previous studies we have shown development of prediabetes in rats maintained on a high-calorie diet [10-12]. The aim of this work was to compare the performance of prediabetes in male and female under development of obesity and the impact of prophylactic administration bionanocomposite under the possibility of the state of hyperglycemia.

#### Materials and methods.

##### Animal care and experimental procedures

Experiments were carried out on outbred female and male rats initially weighing 150-170 g. Research was conducted according to with the standards of the Convention on Bioethics of the Council of Europe's 'Europe