МАТЕРІАЛИ МІЖНАРОДНОЇ НАУКОВОЇ КОНФЕРЕНЦІЇ

КОНЦЕПЦІЯ СУЧАСНОЇ ФАРМАЦІЇ ТА МЕДИЦИНИ: РОЗВИТОК БІОХІМІЇ, БІОТЕХНОЛОГІЙ ТА БІОМЕДИЧНОЇ ІНЖЕНЕРІЇ

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М. ПОЛТАВА, УКРАЇНА

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Міжнародний Центр Наукових Досліджень

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м. Полтава, Україна

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МІКРОБІОЛОГІЯ, БІОЛОГІЯ ЛЮДИНИ І БІОЛОГІЧНА АНТРОПОЛОГІЯ, АНАТОМІЯ ТА ФІЗІОЛОГІЯ ЛЮДИНИ

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FEATURES OF THE EXPRESSION OF THE TRANSCRIPTION FACTOR NF-κB IN EXPERIMENTAL DIABETES MELLITUS AND ADMINISTRATION OF NONSPECIFIC BLOCKERS OF TNFα.

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Type I diabetes mellitus (T1D) is one of the most common non-communicable diseases in the world and is one of the three diseases (atherosclerosis, cancer and diabetes) that lead to disability. This pathology is considered as a multifactorial,

polygenic autoimmune disease, in the development of which special attention should be paid to the relationship of gut-associated lymphoid tissue (GALT) and the factors that affect it and can potentiate the development of this pathology. [1]. Critical role may be played by changes in the expression of innate immune receptors by the structures of GALT - pattern-recognizing receptors (PRR), the main ligands for which are pathogen-associated molecular patterns (PAMP) of intestinal microorganisms [2]. Recently, the question of the fact that the contact of representatives of the intestinal eubiota with PRR leads to the modulation of its composition and maintenance of homeostasis, as well as plays a role in regulating the development of GALT. [3] It has been shown that changes in the composition of the intestinal microflora are quite common in people with T1D and in experimental models. [4, 5] However, the mechanisms of intestinal microbiome induction of autoimmune pathology, including T1D, remain unclear. Transcription factor NF-κB controls the expression of more than 500 genes, including genes for immune response, apoptosis and cell cycle, and violations of its regulation cause the development of inflammation, autoimmune and cancer [6]. c-Rel-containing complexes are usually associated with cells of hematopoietic origin. This factor is the main stimulator of production of proinflammatory cytokines IL-1β, IL-6, IL-18, TNFα and an important regulator of differentiation of cells of adaptive immune response, in particular subpopulations of suppressor T-regulatory (Treg) and proinflammatory Th17- and Th1-cells, the main reservoir pool of which is the small intestine, and their imbalance can play a role in triggering the progression of T1D. [7]. It should be noted that among such NF kB - induced cytokines one of the main roles is played by TNFα, the main source of which are macrophages and activated T-lymphocytes GALT [8]. In NOD mice deficient in TNFR1, resistance to the onset of type 1 diabetes is observed, and stroke has a milder course. However, in these animals there is an increase in the amount of Treg and an increase in their suppressor activity. Presumably, the blockade of TNF-signaling is one of the mechanisms of activation of Treg functions and suppression of type 1 diabetes [9]. One of the non-selective TNFα blockers is pentoxifylline.

In experimental studies on 80 male Wistar rats, using modern techniques (morphometric, immunofluorescent, biochemical methods, polymerase chain reaction with real-time reverse transcription (RT-PCR), statistical analysis), we found out the features of expression of transcription factor in GALT cells in rats with experimental streptozotocin-induced diabetes mellitus (EDM) and after administration of pentoxifylline. Administration of streptozotocin to experimental animals led to the development of EDM: for example, by 2nd week of the pathological process, the concentration of glucose in the blood of rats increased 3.1 times (9,78 ± 0,71 mmol / l, $p < 0,05$) compared with control (3,13 ± 0,12 mmol / l). There was polydipsia, hyperphagia and polyuria - the main symptoms characteristic of type 1 diabetes. The study of serial sections of the ileum of control animals, pre-incubated

with monoclonal antibodies to the transcription factor Nf-kB, showed that the development of diabetes was accompanied by a significant increase in the total density of Nf-kB⁺-cells in the lamina propria of villi (LP) and isolated lymphoid follicles (ILF) by 45,5% and 74%, respectively (p <0,05) at 14th day of pathology. The same trend was maintained on the 4th week of EDM development - an increase in the total density of Nf-kB⁺-cells in the LP by 39,4% (p <0,05) compared with the control. (fig.1A) Administration of pentoxifylline to diabetic animals was accompanied by a tendency to decrease the total density of Nf-kB⁺-cells in both morphofunctional zones in both the 2nd and 4th week of EDM development. However, a significant decrease in the total population density of Nf-kB + cells was observed only in the ILF by 19,7% (p <0,05) on day 14 of pathology. (fig.1B)

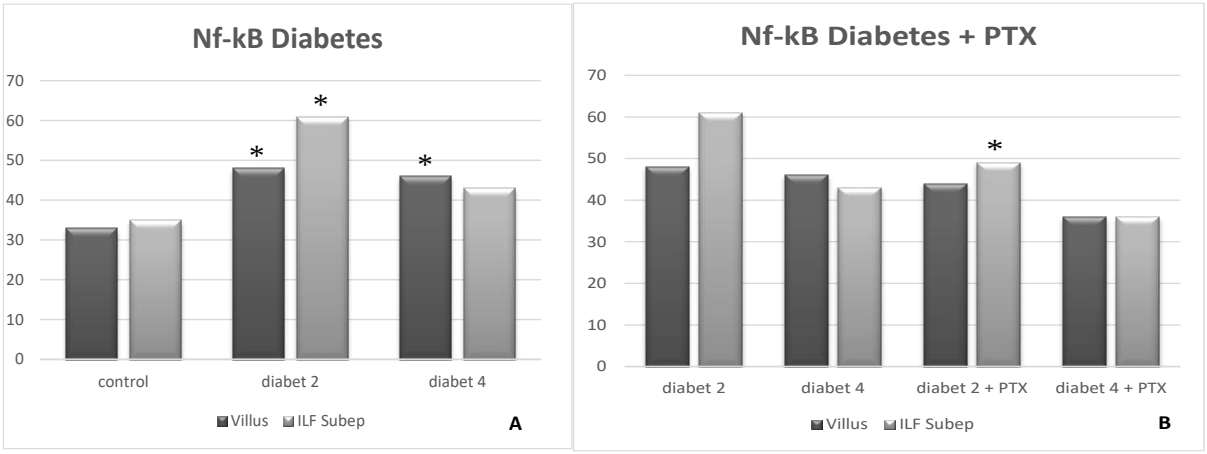

Fig. 1. **The number (on 1 mm²) of Nf-kB+-cells in lamina propria of villus mucous layer (Villus) and in subepithelial zone of isolated lymphoid follicles (ILF Subep). The development of EDM (A). The administration of PTX (B) to experimental animals. Note: * — P < 0. 05**

The study of the relative normalized expression of the Nf-kB1 gene in rat ileal cells at 2nd week of diabetes showed an increase in mRNA concentration by 10,7 times, and at 4th week - by 5,2 times compared with the control group of animals (fig 2A). The transcriptional activity of the c-Rel gene also showed a tendency to increase with the development of EDM. Thus, on the 14th day of diabetes, this figure increased 3,6 times, and on the 28th day – 2,5 times compared with the control group of experimental animals (fig 2C). Administration of pentoxifylline to experimental animals resulted in a 3,2-fold decrease in Nf-kB1 expression at week 2 of EDM development compared with diabetic intact animals (duration of EDM - 2 weeks) and a significant 5-fold decrease in Nf-kB1 mRNA levels at the 4th week of pathology compared with diabetic intact animals (duration of EDM - 4 weeks) (fig 2B). The level of normalized expression of c-Rel on the background of the introduction of pentoxifylline showed significant changes only on the 14th day of the pathological

process - the rate increased 7,8 times compared with diabetic intact animals (duration of EDM - 2 weeks) (fig 2D).

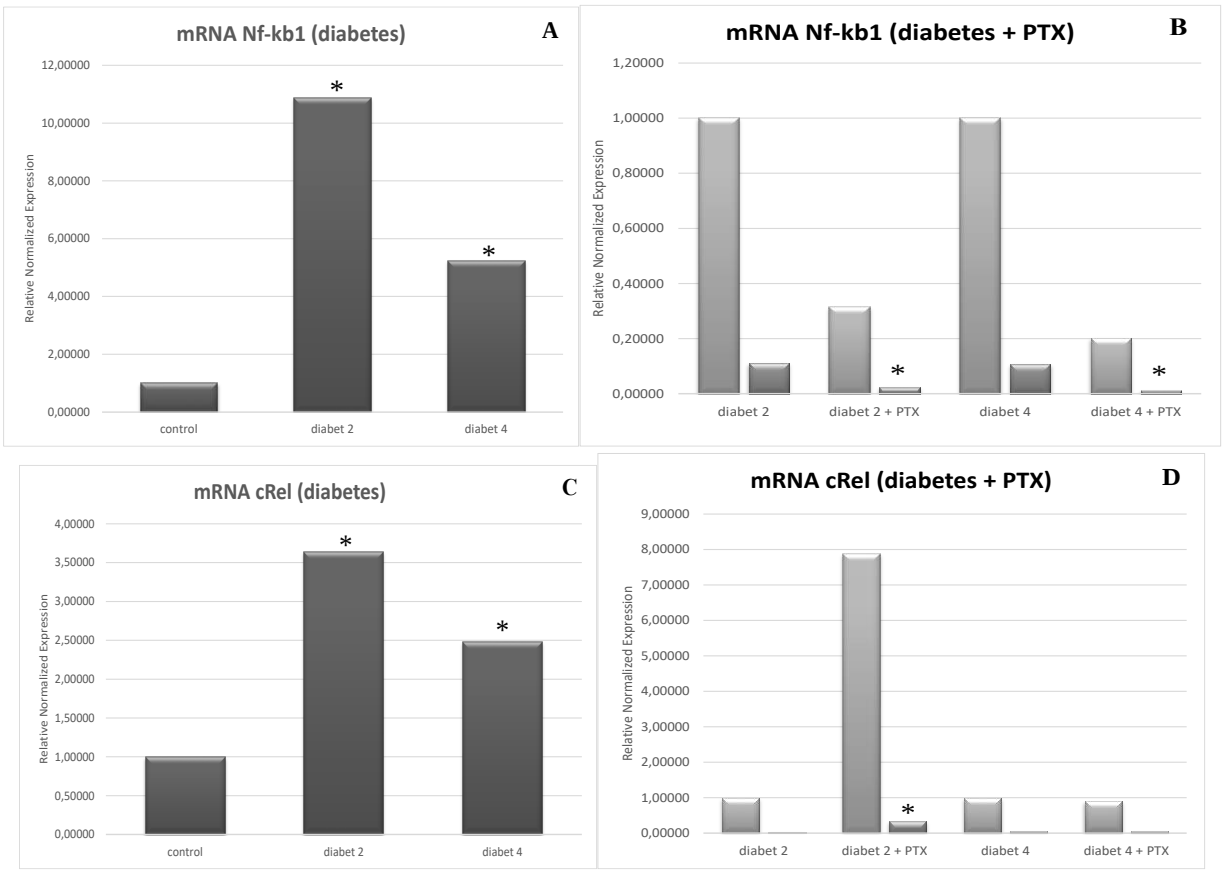

Fig. 2 **Relative normalized expression of mRNA of *Nf-kB1* and *Spi-B* genes in rat ileum ILF cells. Normalization by the ΔΔCt method with the GAPDH reference gene. diabetes 2, diabetes 4 - 2 and 4 week experimental diabetes mellitus, respectively; diabetes 2 + PF, diabetes 4 + PF - after the administration of pentoxifylline to a diabetic animal**

Our results coincide with those of other researchers, because increased expression of Nf kB and increased transcriptional activity of genes Nf-kB1 and c-Rel immune cells of the intestine may affect the differentiation of different subpopulations of T helpers and their production of proinflammatory cytokines, thus acting as a trigger and progression of diabetes. In turn, the introduction of pentoxifylline, as a mild expression blocker, can correct the intensity of pro-inflammatory reactions, including the development of T1D.

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