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THE LEVEL OF NERVE GROWTH FACTOR AND ITS RELATIONSHIP WITH THE CONTENT OF LEUKOCYTES AND MAST CELLS IN EXPERIMENTAL INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME

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Relevance. Interstitial cystitis/painful bladder syndrome (IC/PBS) is a debilitating condition of pain and discomfort in the bladder. Due to the limited number of published studies in this area, there is a need for further research. **Objective:** to evaluate the level of nerve growth factor and its relationship with various types of leukocytes and mast cells of the bladder tissue in animals with experimental models of interstitial cystitis/painful bladder syndrome. **Material and methods.** IC/PBS modeling was performed on 38 female rabbits. The IC/PBS modeling was created by introducing HCl into the bladder (group 1), urine into the wall of the bladder (group 2), and physiological saline (group 3). Nerve growth factor (NGF) was determined by the ELISA method, and white blood cells along with mast cells in tissues were determined by histological processing. **Results.** A statistically significant high level of NGF in blood and urine was observed on the 1st day after IC/PBS initiation in groups 1–3 and in group 2 respectively. Two weeks after the initiation of IC/PBS in animals of group 1 a decrease in the level of FRN in the blood by 29.3% and its increase in urine by 14.3% was observed; in group 2 – an increase by 65.5% ($p < 0.01$) in blood and by 52.7% ($p < 0.01$) in urine was observed and in group 3 – a decrease by 30.8% ($p < 0.05$) in blood and by 30.5% ($p < 0.05$) in urine was observed. The greatest number of leukocytes was determined in the tissue of the bladder in animals of the 1st group. Mast cell infiltration was observed in groups 1 and 2. Correlation between the NGF in blood and urine and between NGF and the number of leukocytes and mast cells was revealed. **Findings.** In IC/PBS, the level of NGF in the blood and urine is increased. Indicators of nerve growth factor in blood and urine are correlated with multidirectional connections. High mast cell infiltration occurs when damage to the integrity of the bladder by urinary toxicity. Nerve growth factor correlates with leukocyte and mast cell infiltration in the bladder tissue. **Conclusion.** During IC/PBS, the level of NGF in the blood and urine is increased. Levels of nerve growth factor in blood and urine are correlated with multidirectional connections. High mast cell infiltration occurs as a response to the damage of the bladder wall integrity caused by urinary toxicity. The level of nerve growth factor correlates with the bladder tissue intensity of infiltration with leukocytes and mast cells.

Keywords: interstitial cystitis/painful bladder syndrome; nerve growth factor; experimental model; white blood cells; mast cells.

УРОВЕНЬ ФАКТОРА РОСТА НЕРВОВ И ЕГО СВЯЗЬ С СОДЕРЖАНИЕМ ЛЕЙКОЦИТОВ И ТУЧНЫХ КЛЕТОК ПРИ ЭКСПЕРИМЕНТАЛЬНОМ ИНТЕРСТИЦИАЛЬНОМ ЦИСТИТЕ/СИНДРОМЕ БОЛЕЗНЕННОГО МОЧЕВОГО ПУЗЫРЯ

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Целью настоящего исследования явилось изучение концентрации фактора роста нервов в моче и крови и содержания лейкоцитов и тучных клеток в ткани мочевого пузыря животных с экспериментальным интерстициальным циститом/синдромом болезненного мочевого пузыря (ИЦ/СБМП). ИЦ/СБМП моде-

лировали на 38 кроликах-самках путем введения в мочевой пузырь соляной кислоты (1-я группа), мочи в стенку мочевого пузыря (2-я группа), изотонического раствора натрия хлорида в стенку мочевого пузыря (3-я группа). В 1-е сутки после инициации ИЦ/СБМП отмечено статистически значимое повышение уровня фактора роста нервов в крови по сравнению с контролем у животных всех трех экспериментальных групп, а в моче — у животных 2-й группы. Через 14 сут после инициации ИЦ/СБМП у животных 1-й группы выявлено снижение уровня фактора роста нервов в крови на 29,3 % и повышение в моче на 14,3 %; во 2-й группе — увеличение на 65,5 % ($p < 0,01$) в крови и на 52,7 % ($p < 0,01$) в моче; в 3-й группе — снижение на 30,8 % ($p < 0,05$) в крови и на 30,5 % ($p < 0,05$) в моче. Наибольшее количество лейкоцитов определяли в ткани мочевого пузыря у животных 1-й группы. Инфильтрацию ткани стенки мочевого пузыря тучными клетками наблюдали у животных 1-й и 2-й групп. Выявлены корреляционные связи между уровнем фактора роста нервов в крови и моче и между уровнем фактора роста нервов и количеством лейкоцитов и тучных клеток. **Выводы**. При ИЦ/СБМП уровень фактора роста нервов в крови и моче повышен. Содержание фактора роста нервов в крови и моче коррелирует между собой разнонаправленно. Выраженная инфильтрация тучных клеток наблюдается при повреждении целостности стенки мочевого пузыря. Уровень фактора роста нервов коррелирует с интенсивностью инфильтрации лейкоцитами и тучными клетками ткани мочевого пузыря.

Ключевые слова: интерстициальный цистит/синдром болезненного мочевого пузыря; фактор роста нервов; экспериментальная модель; лейкоциты; тучные клетки.

INTRODUCTION

Fundamental and clinical studies of interstitial cystitis/painful bladder syndrome (IC/PBS) have been performed. The prevalence of IC/PBS is 10.6 cases per 100,000 adults, and the disease is more often registered in women than in men [1]. The main clinical manifestations of the disease include debilitating pain in the bladder, aggravated bladder filling, and impaired urination [2]. The significance of IC/PBS is determined not only by its high frequency but also by a significant deterioration in the psychoemotional condition and the quality of life of patients [3].

The causes of IC/PBS are not fully understood. Possible pathophysiological mechanisms of its development include epithelial dysfunction, mast cell activation, neurogenic inflammation, autoimmune processes, and latent infection. The IC/PBS diagnosis is a "diagnosis by exclusion" when other possible causes of pain in the bladder are absent [4]. A significant number of studies search for potential biomarkers of the disease. In this regard, determination of nerve growth factor (NGF) is of great interest. NGF is a secreted protein necessary for the development of peripheral sensory neurons [5, 6]. Elevated blood levels of NGF were detected in animals with experimental pancreatitis and peripheral neuropathies [7]. In adults, sympathetic ganglial neurons can express NGF receptors, particularly in chronic inflammation [8]. In inflammatory diseases of the lower urinary tract, the level of NGF in the bladder tissue and in the urine increases [6, 9]. One of possible reasons for the development of IC/PBS is the activation of mast cells, whose count in the bladder wall increases with the disease [10]. In various models of cystitis in small laboratory animals (rodents), a significant increase in the number of mast cells and an increase in their functional activity have been revealed [11, 12]. The results obtained in this research and other studies indicate the prospect of their continuation. However, the number of publications related to the identification of potential biomarkers of IC/PBS is limited, especially in experimental models, and many questions remain unexplored. This circumstance determines the relevance of this study.

The study aimed to evaluate the level of NGF and its relationship with the level of various types of leukocytes and mast cells in the tissue of the bladder in animals with different experimental models of IC/PBS.

MATERIALS AND METHODS

IC/PBS modeling was performed on 38 white New Zealand female rabbits weighing 1500–2000 g. When keeping animals and conducting experimental studies, the rules for care and use of laboratory animals were observed (NIH Guide for the Care and Use of Laboratory Animals) [13].

IC/PBS was modeled in several ways, and the animals were divided into four groups (Table 1).

Hydrochloric acid (HCl), urine, and isotonic sodium chloride solution (NaCl) were used to simulate IC/PBS. In Group 1 animals, IC/PBS was induced by intravesical instillation of HCl (0.2 ml 0.5% HCl). In animals of Group 2, the IC/PBS model was created based on one of the hypotheses of IC development, according to which urinary toxicity leads to the damage of the glycosami-

Table 1 / Таблица 1

Methods for modeling interstitial cystitis / painful bladder syndrome
Способы моделирования интерстициального цистита/синдрома болезненного мочевого пузыря

Study group	Number of animals, *n*	Method for modeling interstitial cystitis / painful bladder syndrome
1	8	Injection of a 0.5% hydrochloric acid solution into the bladder
2	15	Injection into the bladder wall of urine taken from the bladder of an animal
3	7	Injection of isotonic sodium chloride solution into the bladder wall
4	8	Intact (control)

noglycan layer of urothelium [14]. Rabbits underwent suprapubic incision, after which urine obtained from the bladder was injected under the mucous layer of the bladder with a 30-gauge needle syringe with a volume of 0.5 ml. A total of 10 ml 0.9% NaCl were injected into the bladder wall to animals of Group 3.

The NGF level was determined by enzyme-linked immunosorbent assay using an Emax® NGF kit in blood and urine using a Medispec 6000M apparatus (Israel). The measurements were performed 1 and 14 days after the modeling of IC/PBS.

Animals were killed on day 14 after modeling the disease by administrating pentobarbital at a dose of 200 mg/kg to assess the level of blood cells in the tissues of animals. Then, a midline transabdominal incision and cystectomy were performed. Bladder tissue samples were embedded in paraffin; 4-micron-thick sections were prepared using a microtome. Then, the samples were stained with hematoxylin and eosin to estimate the number of leukocytes and stained with toluidine blue to estimate the amount of mast cells. An Olympus Bx 50 light microscope and an Olympus PM10SP camera system were used to view the microslides. Each cross-section was divided into 10 sections. The level of leukocytes and the degree of mast cell infiltration were evaluated in each section using the following scale: 0, no extravascular leukocytes or mast cells; 1, less than 20 leukocytes and mast cells; 2, 20–45 leukocytes and mast cells; 3, more than 45 leukocytes and mast cells. The scores of all 10 sections were added, divided by 30 (the maximum possible score), and multiplied by 100. The leukocyte and mast cell scores for each bladder were the average of three sections studied. The leukocytes and mast cells were counted under an optical magnification of ×200 [15, 16].

Statistical processing of the data obtained was performed using the programs Statistica for Windows 8.0 and Microsoft Excel. The mean value and standard deviation of the mean were calculated. Differences were considered significant at $p < 0.05$. The correlation dependence between the indicators was determined by the Pearson correlation coefficient.

RESULTS

Table 2 presents the results of the study of the NGF level in the experimental groups.

The NGF level in the blood on day 1 after the IC/PBS modeling was statistically higher in all experimental groups compared with the control. Thus, in Group 1,

Table 2 / Таблица 2

The level of nerve growth factor in the blood and urine of experimental animals on the 1st and 14th day after the initiation of the IC/PBS, *M* ± σ
Уровень фактора роста нервов в крови и моче экспериментальных животных в 1-е и 14-е сутки после инициации ИЦ/СБМП, *M* ± σ

Group	Day 1		Day 14	
	blood, ng/ml	urine, ng/ml	blood, ng/ml	urine, ng/ml
1 (*n* = 8)	17.64 ± 8.43* (10.2; 48.3)	10.51 ± 1.06 (8.5; 13.2)	13.64 ± 0.86* (12.1; 15.3)	12.26 ± 1.83 (9.8; 17.4)
2 (*n* = 15)	24.33 ± 16.30* (6.9; 68)	30.39 ± 27.46* (9.6; 155.1)	70.62 ± 21.63*, ** (42.5; 125.8)	64.26 ± 22.84*, ** (26.4; 155.1)
3 (*n* = 7)	12.47 ± 5.02* (4.7; 21.8)	13.3 ± 1.91 (9.6; 16.6)	9.53 ± 0.95* (7.8; 10.9)	10.19 ± 1.01 (8.5; 12.0)
4 (*n* = 8)	6.99 ± 1.84 (4.3; 9.4)	9.65 ± 0.6 (8.5; 10.7)		

Note: *$p < 0.05$ compared with the values in Group 4 (control); **$p < 0.05$ compared with the values in Groups 1, 3, and 4 and with the value on day 1 of the study.

Table 3 / Таблица 3

The level of white blood cells and mast cells in the bladder wall of the experimental animals on the 14th day after the initiation of the IC/PBS, $M \pm \sigma$

Содержание лейкоцитов и тучных клеток в стенке мочевого пузыря у экспериментальных животных через 14 суток после инициации ИЦ/СБМП, $M \pm \sigma$

Group	Cell types			
	neutrophils	lymphocytes	eosinophils	mast cells
1 (n = 8)	89.375 ± 14.927** (68; 112)	48.375 ± 7.614*, *** (36; 59)	2.125 ± 3.226*, ** (0; 8)	1.125 ± 1.642 (0; 4)
2 (n = 10)	0.866 ± 1.884 (0; 6)	29.866 ± 10.183*, *** (12; 49)	0.333 ± 0.899 (0; 3)	14.200 ± 5.796**** (3; 26)
3 (n = 7)	1.428 ± 2.699 (0; 7)	2.285 ± 3.728* (0; 10)	0.142 ± 0.377* (0; 1)	0
4 (n = 7)	0	0.375 ± 1.060 (0; 3)	0.375 ± 0.744 (0; 2)	0

Note: *$p < 0.05$ compared with the values in Group 4 (control); **$p < 0.05$ compared with the values in Groups 2 and 3; ***$p < 0.05$ compared with the values in Groups 3 and 4; ****$p < 0.01$ compared with the values in Group 1.

Table 4 / Таблица 4

The results of a correlation analysis between the NGF level in blood, urine and white blood cells, mast cells count in the bladder wall in experimental animals on the 14 days after the initiation of IC / PBS

Результаты корреляционного анализа содержания ФРН в крови и моче и количества лейкоцитов и тучных клеток в стенке мочевого пузыря у экспериментальных животных через 14 суток после инициации ИЦ/СБМП

Group	Cell types			
	NGF neutrophils in blood/urine	NGF lymphocytes in blood/urine	NGF eosinophils in blood/urine	NGF mast cells in blood/urine
1 (n = 8)	–0.864/–0.367	–0.749/–0.805	–0.018/–0.304	+0.013/+0.410
2 (n = 10)	–0.224/–0.007	–0.481/+0.221	–0.739/+0.520	–0.260/–0.178
3 (n = 7)	–0.015/+0.331	+0.044/+0.325	+0.523/-0.573	–
4 (n = 7)	–	–0.507/–0.025	–0.652/–0.563	–

Note. NGF is nerve growth factor; r is the correlation coefficient.

the NGF level exceeded the control by 60.4% ($p < 0.01$), by 71.3% in Group 2 ($p < 0.01$), and by 43.9% in Group 3 ($p < 0.05$). The NGF level in the urine of Group 2 during this follow-up period was statistically significantly higher than that in the control (by 68.2%, $p < 0.01$), whereas in other groups, the difference was not statistically significant. Fourteen days after the disease initiation, the NGF blood level in all experimental groups was higher compared with that of the control group. In Group 1, the difference with intact animals amounted to 48.7% ($p < 0.05$), 90.1% in Group 2 ($p < 0.001$), and 26.6% in Group 3. An almost identical result was noted when analyzing the NGF level in animal urine. Compared with Group 4, the urine biomarker levels were higher by 21.3%, 85.0%, and 5.3% in Groups 1, 2 ($p < 0.001$), and 3, respectively.

An intragroup dynamic analysis of NGF levels at different periods of the study (days 1–14) showed that in Group 1, the blood biomarker level decreased by 29.3% and increased in urine by 14.3%. In Group 2, the level of NGF increased by 65.5% in the blood and by 52.7% in the urine on day 14 of the study in comparison with day 1 ($p < 0.01$). In the animals of Group 3, the NGF level 14 days after the disease initiation decreased by 30.8% and 30.5% in the blood and urine, respectively ($p < 0.05$).

Leukocyte infiltration of the bladder wall tissues was the highest in the animals of Group 1, whereas the highest concentration of mast cells was observed in the animals of Group 2 (Table 3).

The average number of all types of leukocytes in the bladder wall tissues in the animals of Group 1 was statistically significantly higher than that in Groups 2, 3, and 4 ($p < 0.001$). Mast cells were determined in the bladder wall only of the animals in Groups 1 and 2, with Group 2 yielding a significantly and statistically higher number.

A study of the relationship between NGF level and the number of leukocytes and mast cells in the bladder wall revealed multidirectional trends (Table 4).

In animals of Group 1, a negative correlation was observed between the level of NGF in the blood and urine and the degree of leukocyte infiltration of the bladder wall (neutrophils, eosinophils, and lymphocytes), whereas a positive correlation was noted between the level of NGF in the blood and urine and the level of mast cells in the bladder wall. In Group 2 animals, a moderate negative correlation was revealed between the blood and urine levels of NGF and the count of mast cells. Between the lymphocyte level in the animals of this group and NGF level of the blood, a moderate negative correlation and a weak positive correlation were noted between the lymphocyte level and the level of NGF in the urine. In the animals of Group 3, a significant correlation was observed between the NGF level and the number of eosinophils. In intact animals, the blood and urine levels of NGF were negatively correlated with the concentration of lymphocytes and eosinophils.

DISCUSSION

The study results revealed an increased concentration of NGF in the blood for all variants of the IC/PBS model on day 1 after the disease initiation. The increase in the biomarker level was especially pronounced in the model with injected urine into the bladder wall. Our results correspond with data from other studies [17]. Reports indicate an increase in the level of NGF in the bladder tissues in experimental models of IC in rats [9, 17–19]. Researchers also believe that inflammation increases NGF expression, and this condition features a significant pathogenetic value in the development of IC/PBS [9, 19].

NGF can affect afferent fibers of the bladder and is responsible for the growth of sensory neurons and for the normal function of visceral sensory and motor neurons in adults [5, 9]. Basic scientific studies revealed that inflammation causes neuroplasticity, which results in an increase in the NGF level in the bladder tissue and initiation of IC/PBS [5, 20].

Clinical and experimental data indicate an increase in NGF levels in the bladder tissue and urine of IC/PBS patients [5, 9, 18]. We also revealed an increased level of NGF in the urine of animals with different models of IC/PBS. However, a statistically significant high level of NGF was noted only in the variant with injection of urine into the bladder wall.

A study of the NGF level change on days 1 and 14 after IC/PBS initiation showed a statistically significant increase in NGF level in the disease model triggered by introduction of urine into the bladder wall. An increase in the NGF level in blood and urine with IC/PBS was apparently due to inflammatory components, and a pronounced increase in the biomarker level in animals with a model of urine injection into the bladder wall was due to chronic inflammation and toxicity of urine components.

This study presents the results of determining the level of leukocytes (neutrophils, lymphocytes, and eosinophils) and mast cells in the bladder tissue of animals with different variants of IC/PBS model. A high level of mast cell infiltration was detected in the chemical model (Group 1, injection of HCl into the bladder wall) and the model with urinary toxicity (Group 2, injection of urine into the bladder wall). In the animal model of urinary toxicity, mast cell activity was statistically significantly higher than that in the chemical model of the disease ($p < 0.001$).

Mast cells are currently recognized as regulatory and effector cells of both innate and acquired immunity [21]. Their diverse functions depend on their ability to respond to various stimuli and secrete biologically active products with pro-inflammatory, anti-inflammatory, and/or immunosuppressive properties. Mast cells play an important role in allergic inflammation mediated by immunoglobulins. As innate immune defenders, mast cells recognize microbial agents (bacterial, viral, parasitic, and fungal) and endogenous factors resulting from cell damage [21]. This condition probably explains the absence of mast cell infiltration in rabbits of Groups 3 and 4. At the same time, the statistically significant activity of mast cells in the animals of Group 2 may indicate that with this modeling variant, the urothelium of the bladder is damaged severely, and mast cells respond with high infiltration.

CONCLUSIONS

A statistically significant increase in the blood level of NGF was revealed in animals with experimental IC/PBS caused by injection of HCl into the bladder cavity and NaCl and urine into the submucous membrane of the bladder wall. A statistically significant increase in the NGF level in the urine was noted when modeling IC/PBS by injection of urine into the bladder wall ($p < 0.001$). The values of NGF in blood and urine correlated with each other with multidirectional bonds. High mast cell infiltration occurred during damage to the bladder integrity due to urinary toxicity. A correlation exists between NGF level and leukocyte and mast cell infiltration.

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