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## BIOCHEMICAL PARAMETERS OF RAT'S BLOOD UNDER THE CHRONIC OPIOID EXPOSURE

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The purpose of the study was to establish changes in some biochemical parameters of rat's blood, which indicate the functional state of the kidney with prolonged administration of nalbuphine in the experiment. As a result of the study, it was found that the administration of small doses of nalbuphine during a 12-week experiment leads to impaired renal filtration function, which was first detected after 4 weeks of nalbuphine administration, reaches its maximum manifestation after 8 weeks of nalbuphine administration and stabilizes in the following terms, as evidenced by the dynamics of creatinine and urea in the serum of rats. Impaired renal reabsorption function was first detected after 2 weeks of nalbuphine administration and acquires a pronounced manifestation after 8, 10 and 12 weeks of the experiment, as evidenced by the dynamics of calcium and phosphorus in the rats' serum.

**Key words:** kidney, urea, creatinine, phosphorus, calcium, serum, nalbuphine, rat.

## І.В. Вільхова, Л.Р. Матешук-Вацеба, М.В. Логаш, О.В. Канцер' БІОХІМІЧНІ ПОКАЗНИКИ КРОВІ ЩУРІВ ПРИ ХРОНІЧНОМУ ОПОЇДНОМУ ВПЛИВІ

Метою дослідження було встановлення змін деяких біохімічних показників крові щура, які свідчать про функціональний стан нирки, при тривалому введенні налбуфіну в експерименті. У результаті проведеного дослідження встановлено, що введення малих доз налбуфіну впродовж 12-ти тижневого експерименту призводить до порушення фільтраційної функції нирок, котре вперше виявлено через 4 тижні введення налбуфіну, максимального прояву набуває через 8 тижнів введення налбуфіну та в наступних термінах стабілізується, про що свідчить динаміка показників креатиніну та сечовини в сироватці крові щурів. Порушення реабсорбційної функції нирок вперше виявлено через 2 тижні введення налбуфіну та вираженого прояву набуває через 8, 10 та 12 тижнів експерименту, про що свідчить динаміка показників кальцію та фосфору в сироватці крові щурів.

**Ключові слова:** нирка, сечовина, креатинін, фосфор, кальцій, сироватка крові, налбуфін, щур.

*The work is a fragment of the research project "Morpho-functional features of organs in the pre- and postnatal periods of ontogenesis under the influence of opioids, food supplements, reconstructive surgery and obesity", state registration No. 0120U002129.*

The problem of drug addiction remains one of the most pressing problems of modern society. The United Nations Office on Drugs and Crime has published the World Drug Report 2018, which states that about 275 million people (almost 5.6 % of the world's population) between the ages of 15 and 64 have used drugs at least once in their lifetime, and opium production increased by 65 % in 2016–2017. Opioids are also used to obtain an analgesic effect in patients [6]. The current issue is the safety and effectiveness of narcotic drugs for the treatment of chronic and acute non-cancerous pain, which lasts more than 90 days [12, 13]. The negative effect of the use of drugs today creates not only a serious medical and social, but also economic problem. Experimental studies of the effects of opioids on organs and systems of the body are currently a common trend among morphological works [14]. Recently, many researchers have been studying the morphology of organs and systems with the administration of nalbuphine in the experiment [8]. The experiment uses different models and doses of the drug to study the effects of nalbuphine on organs and systems, due to the specific objectives of the study [10]. Changes in the structure of the kidney under the influence of opioid substances in drug-addicted people, as well as in an experiment on rats have been studied [9]. Of particular interest are works that study the structural and functional changes of the organs with the use of opioid analgesics [11]. In conclusion, there are a number of unresolved issues related to the structural restructuring of the urinary system, including the kidneys, under the influence of opioid drugs.

**The purpose** of the study was to establish changes in some biochemical parameters of rat's blood, which indicate the functional state of the kidney with prolonged administration of nalbuphine.

**Materials and methods.** The study material was 70 white sexually mature male rats weighing 180–260 g. The animals were kept in a vivarium and the study was carried out in accordance with the "Rules for carrying out work using experimental animals", which corresponds to the provisions of the Declaration of Helsinki. Animal experiments were performed in accordance with the provisions of the European Community Directive of November 24, 1986. The performed study meets the ethical requirements according to the Order of the Ministry of Health of Ukraine No. 231 of 01.11.2000 (Protocol

No. 2 of February 20, 2012), established by the Commission on Bioethics of Danylo Halytsky Lviv National Medical University.

Experimental animals were injected nalbuphine (Nalbuphine injection, 20 mg) daily, intramuscularly, for twelve weeks. During the first two weeks of the experiment, the dose of nalbuphine was 0.212 mg/kg (experimental group 1), from the second to the fourth week, animals were administered nalbuphine at the dose of 0.225 mg/kg (experimental group 2), from the fourth to the sixth week – 0.252 mg/kg (experimental group 3), from the sixth to the eighth week – 0.260 mg/kg (experimental group 4), from the eighth to the tenth week – 0.283 mg/kg (experimental group 5), from the tenth to the twelfth week – 0.3 mg/kg (experimental group 6). The control group received intramuscular injections of saline for twelve weeks. Nalbuphine was administered in ascending doses every two weeks. Thus, a model of chronic opioid exposure was created [2]. Blood for the study was sampled after intraperitoneal administration of sodium thiopental from the inferior vena cava. Each animal was pre-labeled and weighed. Total protein, urea, creatinine, calcium, and phosphorus were determined in the blood serum of experimental animals. Total serum protein assay was carried out by biuret test (“Filisit-Diagnostics” kit of reagents, Czech Republic), serum creatinine assay – using the Jaffe reaction (“Filisit-Diagnostics” kit of reagents, Czech Republic), serum urea assay – by color reaction with diacetyl monoxime (Bio-Lachema-Test kit), serum calcium assay – using photometric assay of total calcium in biological fluids (“Filisit-Diagnostics”, Czech Republic), serum phosphorus assay – using photometric assay of phosphorus in biological fluids (“Filisit-Diagnostics”, Czech Republic) [3].

All the data were tested for the normality of the distribution using the coefficients of asymmetry and excess, as well as using the Shapiro-Wilk test (confidence level  $p < 0.1$ ). All the data obtained had a normal distribution pattern. The data were presented as  $M \pm SD$ , where  $M$  is the mean value and  $SD$  is the standard deviation. Despite the normal nature of the data distribution, due to the significant difference in the variances of different groups in all parameters, the nonparametric Kruskal–Wallis H-test was used to determine the statistical reliability of the difference between the data in multiple comparisons, followed by post hoc analysis using the Dunn’s test. Pearson's correlation coefficient  $R$  was used for correlation analysis. The results were considered reliable at  $p < 0.05$ .

All statistical calculations were performed using RStudio v.1.1.442 and R Commander v. 2.4-4 software.

**Results of the study and their discussion.** Because of the study, the biochemical parameters of total protein, urea, creatinine, calcium and phosphorus in the serum of rats at twelve weeks of administration of nalbuphine were established.

Serum protein values tended to decrease from the second to the eighth week of the experiment compared to the control group, which was  $65.90 \pm 4.58$  g/L, but this trend was not statistically confirmed (table 1).

Table 1

**Dynamics of biochemical parameters of the rats' serum at 12-week administration of small doses of nalbuphine,  $M \pm SD$ ,  $n=10$**

Parameters	Control	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
Total protein, g/L	$65.90 \pm 4.58$	$62.40 \pm 3.81$	$62.40 \pm 2.50$	$64.40 \pm 3.57$	$62.10 \pm 2.13$	$74.90 \pm 3.81^{***}$	$67.70 \pm 2.16$
Urea, $\mu\text{mol/L}$	$5.91 \pm 0.72$	$6.22 \pm 0.47$	$5.73 \pm 0.35$	$7.62 \pm 0.73^{***}$	$11.08 \pm 0.64^{***}$	$8.90 \pm 0.90^{***}$	$8.84 \pm 0.84^{***}$
Creatinine, $\mu\text{mol/L}$	$48.35 \pm 10.83$	$53.02 \pm 7.56$	$78.98 \pm 4.54^{***}$	$107.89 \pm 7.36^{***}$	$109.60 \pm 6.23^{***}$	$94.28 \pm 2.98^{***}$	$62.84 \pm 4.02^{**}$
Calcium, $\mu\text{mol/L}$	$2.34 \pm 0.16$	$2.16 \pm 0.09^*$	$2.39 \pm 0.10$	$2.39 \pm 0.09$	$2.03 \pm 0.07^{***}$	$1.98 \pm 0.08^{***}$	$1.89 \pm 0.06^{***}$
Phosphorus, $\mu\text{mol/L}$	$2.25 \pm 0.17$	$2.42 \pm 0.05$	$2.32 \pm 0.11$	$2.12 \pm 0.12$	$1.93 \pm 0.08^{***}$	$2.04 \pm 0.11^*$	$1.98 \pm 0.15^{***}$

Note: \* –  $p < 0.01$ ; \*\* –  $p < 0.001$ ; \*\*\* –  $p < 0.0001$  compared to the control

The serum protein index increases sharply after ten weeks of the experiment to a value of  $74.90 \pm 3.81$  g/L, which was statistically significant both when compared with the control group and with the parameters of previous terms ( $p < 0.0001$ ). However, at the next stage of the study, after twelve weeks of the experiment, the protein level decreased almost to the level of the control group and amounted to  $67.70 \pm 2.16$  g/L (Fig. 1).

An increase in serum creatinine compared to the mean control value was observed after two weeks of the experiment, although at this time it was not confirmed statistically ( $p=0.71$ ). At all subsequent periods, there was a reliable and significant increase in the creatinine index.

Changes in serum urea after two and four weeks of the experiment were insignificant and did not have a statistically significant difference when compared with the control group (Fig. 2).

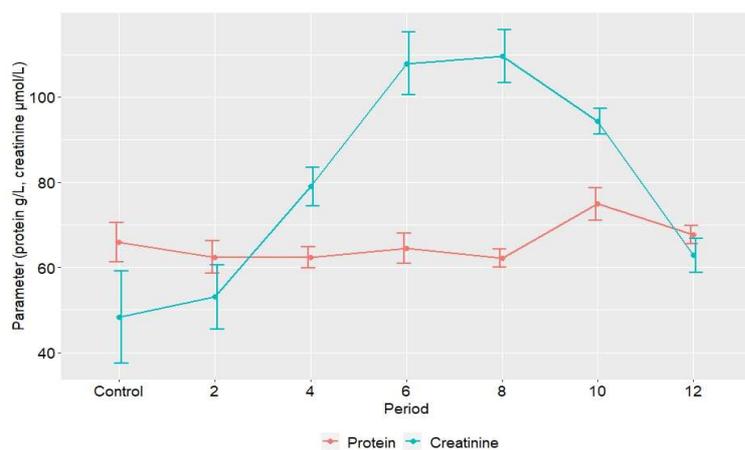


Fig. 1. Changes in total protein and creatinine in rats' serum at 12 weeks of low-dose nalbuphine administration.

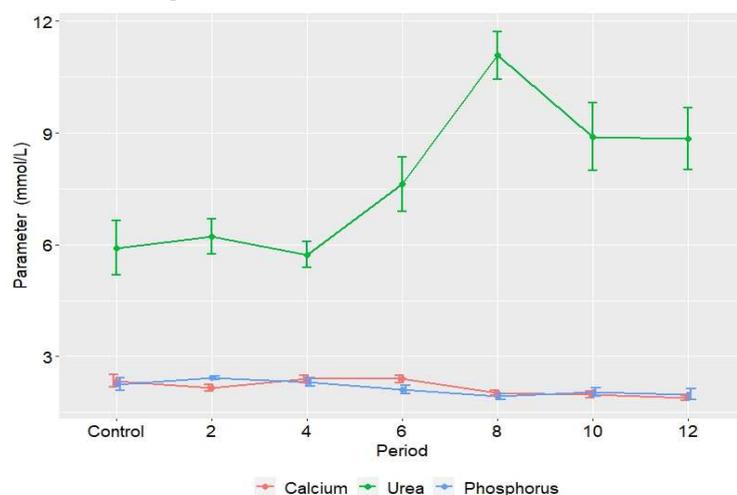


Fig. 2. Changes in urea, calcium and phosphorus in rat's serum at 12 weeks of low-dose nalbuphine administration.

of the experiment, serum creatinine levels decreased sharply to  $62.84 \pm 4.02 \mu\text{mol/L}$ , which was significantly lower than in the tenth week of the experiment ( $p < 0.0001$ ), but remained significantly higher than in the control group ( $p < 0.001$ ).

A significant, direct, pronounced relationship was found between the values of urea and serum creatinine ( $R=60.5$ ,  $p < 0.001$ ). That is, with a higher value of the blood urea index, there is a tendency to increase the value of the serum creatinine index.

Since after the tenth and twelfth weeks of the experiment there is a decrease in creatinine and urea levels compared to the eighth week of the experiment, it can be assumed that administration of nalbuphine more than for more than eight weeks does not lead to progression of disturbance of nitrogen excretory function of a kidney. Such a relative stabilization of the functional state of the kidney may indicate the adaptation of renal structures to the action of nalbuphine after eight weeks of drug administration and the cessation of progression of renal corpuscle lesions.

The rat's blood calcium index tended to decrease with some fluctuations compared to the control group throughout the study. Thus, after two weeks of the experiment, the level of calcium decreased to  $2.16 \pm 0.09 \text{ mmol/L}$  with a control group indicator of  $2.34 \pm 0.16 \text{ mmol/L}$ , and this decrease was statistically significant ( $p < 0.01$ ). However, after four and six weeks of the experiment, calcium values stabilized at the level of the control group and amounted to  $2.39 \pm 0.10 \text{ mmol/L}$  and  $2.39 \pm 0.09 \text{ mmol/L}$ , respectively, the difference in comparison with the control group was not statistically confirmed ( $p=0.89$  and  $p=0.91$ , respectively). After eight, ten, and twelve weeks of the experiment, a significant decrease in rat serum calcium was observed relative to the control group ( $p < 0.0001$  for each period). The serum calcium level of rats was 1.15 times lower after eight weeks of the experiment compared with the control group, and 1.18 times lower after ten weeks. After twelve weeks, the calcium index reaches the lowest recorded value during the experiment at  $1.89 \pm 0.06 \text{ mmol/L}$ , which is 1.23 times less than the value of the control group.

The mean values of phosphorus in the first terms of the study (second, fourth and sixth weeks) ranged within the value of the control group, which was  $2.25 \pm 0.17 \text{ mmol/L}$ . Although, already in the sixth week there was a tendency to decrease and the indicator was  $2.12 \pm 0.12 \text{ mmol/L}$ , but this decrease was not

However, after six weeks of the experiment, the mean value increased to  $7.62 \pm 0.73 \text{ mmol/L}$  against the control group of  $5.91 \pm 0.72 \text{ mmol/L}$ , and this trend was confirmed statistically ( $p < 0.0001$ ). After eight weeks, the urea value reached its maximum value during the experiment and was 1.87 times higher compared to the control group –  $11.08 \pm 0.64 \text{ mmol/L}$  ( $p < 0.0001$ ). After that, there was a tendency to decrease the urea index in the tenth and twelfth weeks of the study and the average values were  $8.90 \pm 0.90 \text{ mmol/L}$  and  $8.84 \pm 0.84 \text{ mmol/L}$ , respectively, which, despite the decrease compared to the eighth week, remained significantly 1.5 times higher than the control group ( $p < 0.0001$ ).

The creatinine index, as well as the rat's serum urea, was acquired the maximum value during the experiment after eight weeks and was  $109.60 \pm 6.23 \text{ mmol/L}$ , which was 2.26 times higher compared to the control group (control group –  $48.35 \pm 10.83 \text{ mmol/L}$ ,  $p < 0.0001$ ). After that, there was a tendency to decrease the creatinine index at the tenth and twelfth weeks of the study, which, despite the decrease compared to the eighth week, remained significantly higher in both 1.95 and 1.29 times, respectively, compared to the control group. After twelve weeks

statistically significant ( $p=0.18$ ). At subsequent periods, the decrease in the phosphorus index value was confirmed statistically compared to the control group and amounted to  $1.93\pm 0.08$  mmol/L at the eighth week,  $2.04\pm 0.11$  mmol/L at the tenth week, and  $1.98\pm 0.15$  mmol/L at the twelfth week, respectively. Serum phosphorus levels in rats was 1.17 times lower after eight weeks of the experiment compared to the control group, 1.1 times lower after ten weeks, and 1.14 times lower after twelve weeks of the experiment.

A significant, direct, pronounced relationship was found between the values of serum phosphorus and calcium ( $R=1.3$ ,  $p<0.001$ ). That is, with a lower value of serum phosphorus, there is a tendency to decrease the value of serum calcium.

The results of the study first showed in the experiment that prolonged administration of even small doses of nalbuphine has a negative effect on the functional state of the kidney, which can be assessed by changes in the biochemical parameters of the blood of the experimental animal. The data obtained on the reduction of serum protein from the second to the eighth week of exposure to nalbuphine, in our opinion, may indicate a loss of protein in the urine as a result of impaired filtration or reabsorption functions of the nephron with the administration of nalbuphine for eight weeks. In the literature it is described that the use of opioids can cause acute kidney damage, decreased glomerular filtration rate [4, 7]. The increase in urea and creatinine with prolonged administration of nalbuphine indicates a violation of the filtration function of the kidney, namely the violation of the excretion of protein metabolism products, which is the result of damage to the renal corpuscles [14]. Based on the data obtained, we can assume that impaired renal filtration function occurs with the administration of nalbuphine for four weeks, because after four weeks of the experiment for the first time there is an increase in creatinine in the serum of rats. The increase in creatinine and urea to the maximum value with the administration of nalbuphine for eight weeks indicates a deepening of the filtration function of the kidney and the greatest damage to the renal corpuscles at this time of the experiment [5]. It is known that 90 % of filtered calcium and phosphates are absorbed in the proximal convoluted tubules by facultative reabsorption. Accordingly, the level of calcium and phosphorus in the serum depends, among other regulatory mechanisms and factors, on the reabsorption function of the kidney, namely on the function of the convoluted tubules of the nephron [1, 15]. The obtained data on the reduction of calcium levels after two weeks of the experiment may indicate the initial manifestations of damage to the convoluted tubules of the kidney and their dysfunction with two weeks of nalbuphine. Restoration of serum calcium to normal values after four and six weeks of the experiment may indicate the accession of compensatory mechanisms of reabsorption function of the kidney. However, a significant persistent decrease in serum calcium and phosphorus levels in the late stages – after eight, ten and twelve weeks of the experiment is a sign of persistent impairment of renal reabsorption function with the nalbuphine administration for more than six weeks.

### Conclusion

As a result of the study, it was found that the administration of small doses of nalbuphine during a twelve-week experiment leads to impaired filtration and reabsorption functions of the kidneys, as indicated by the dynamics of creatinine, urea, calcium and phosphorus in the serum of rats. Impaired renal filtration function was first detected after four weeks of nalbuphine administration, peaked after eight weeks of nalbuphine administration and stabilized in the following terms, as evidenced by the dynamics of creatinine and urea in the serum of rats. Impaired renal resorption function was first detected after two weeks of nalbuphine administration and became more pronounced after eight, ten and twelve weeks of the experiment, as evidenced by the dynamics of calcium and phosphorus in the serum of rats.

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### PECULIARITIES OF THE EFFECT OF A HIGH-CALORIUM DIET ON THE STRUCTURE OF THE SPLEEN ON THE CORRECTION WITH ORLISTAT

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Sodium glutamate is a food additive that is used worldwide in the food industry to enhance taste. The aim of the present study was to determine the morphometric and histological changes of the rat spleen parenchyma in experimental obesity and its correction with orlistat. The study was performed on 66 white rats of reproductive age. Eight weeks after the experimental animals were on a high calorie diet, a significant decrease in the relative area of the white pulp in the spleen parenchyma of white rats of males and females was observed and, accordingly, an increase in the relative area of red pulp, increase the number of secondary lymph nodes, but the zones are not clearly traced, the number of monocytes, macrophages and plasmocytes is increasing, numerous macrophages contain hemosiderin residues in the cytoplasm. Under the conditions of orlistat correction, fewer structural changes in the parenchyma of the spleen were detected.

**Key words:** experiment, spleen, sodium glutamate, ORLISTAT, lymphocyte.

### Т.В. Гарапко, Л.Р. Матешук-Вацеба, А.С. Головацький, У.Є. Підвальна ОСОБЛИВОСТІ ВПЛИВУ ВИСОКОКАЛОРИЙНОЇ ДІЄТИ НА СТРУКТУРУ СЕЛЕЗІНКИ ЗА УМОВ КОРЕКЦІЇ ОРЛІСТАТОМ

Глутамат натрію є харчовою добавкою, яка в усьому світі використовується в харчовій промисловості з метою підсилення смаку. Метою дослідження було вивчення морфометричних та гістологічних змін паренхіми селезінки щурів при впливі на організм глутамату натрію та корекції його дії орлістатом. Дослідження проведено на 66 білих щурах репродуктивного віку. Через вісім тижнів перебування експериментальних тварин на висококалорійній дієті спостерігається достовірне зменшення відносної площі білої пульпи в паренхімі селезінки білих щурів самців та самок та відповідно збільшення відносної площі червоної пульпи, зростання кількості вторинних лімфоїдних вузликів, проте зони прослідковуються не чітко, кількість моноцитів, макрофагів та плазмочитів зростає, численні макрофаги містять у складі цитоплазми залишки гемосидерину. В умовах корекції орлістатом у паренхімі селезінки виявлено менше структурних змін.

**Ключові слова:** експеримент, селезінка, глутамат натрію, орлістат, лімфоцит

*The work is a fragment the research project “Morphological characteristics of internal organs and vascular bed in ontogenesis in the norm and patterns of their restructuring in obesity and the impact on the body of physical factors”. State registration number 0119U102059.*

Sodium glutamate is a food additive that is used worldwide in the food industry to enhance taste [1]. Prolonged use of sodium glutamate causes a number of diseases and complications, the treatment of which causes significant difficulties [3]. Scientists conclude that this food supplement causes metabolic disorders and contributes to the development of obesity [1]. Studies in newborn mice and rats have shown that this supplement over time causes obesity and diabetes, so it is not recommended for use in the production of baby foods [2, 3].