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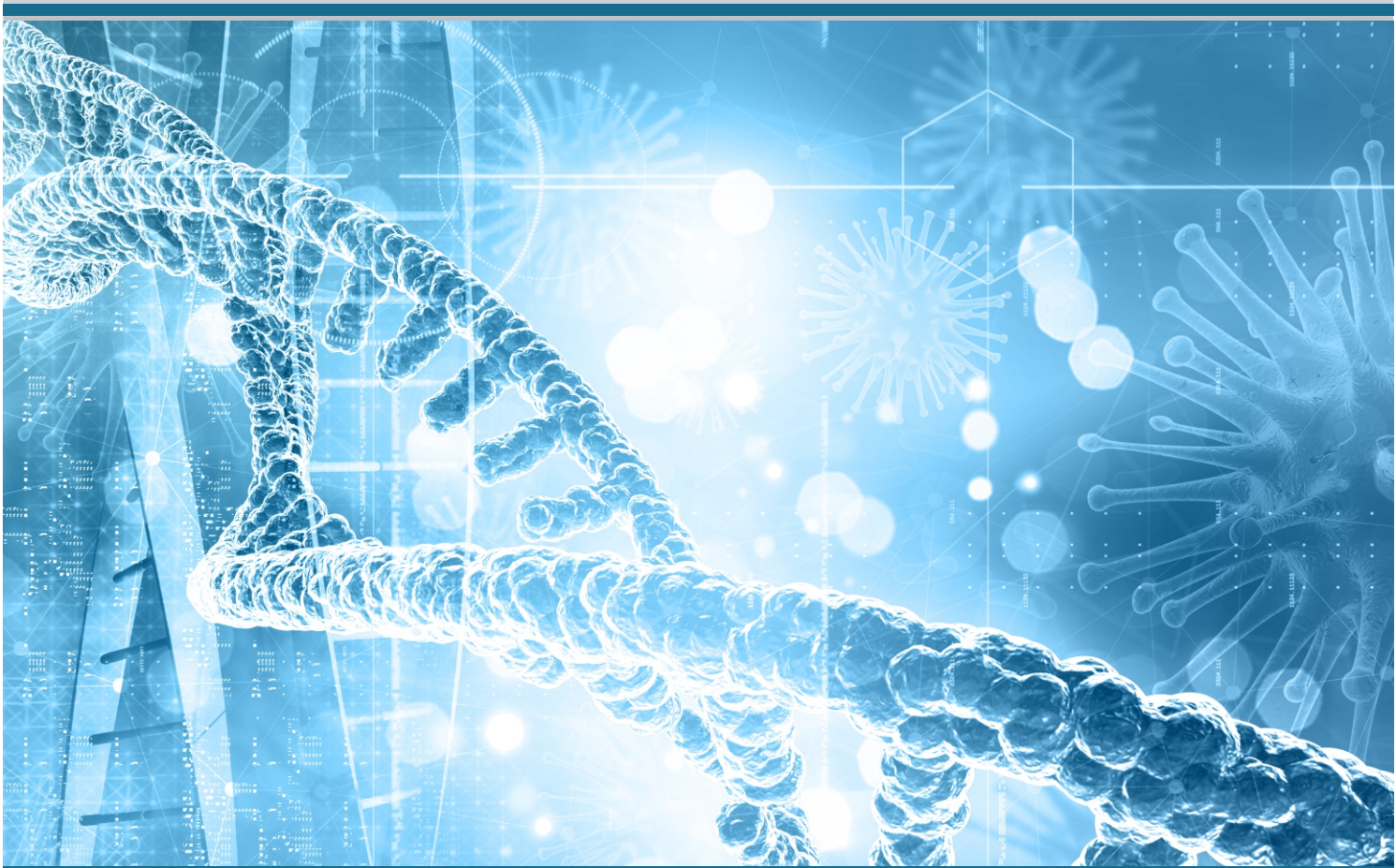
BIOCHEMISTRY AND MOLECULAR BIOLOGY



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пл. Антония Тызенгауза, 7,
230023, г. Гродно, Республика Беларусь,
Институт биохимии биологически активных соединений НАН Беларуси,
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HEMATOLOGICAL AND BIOCHEMICAL STATUS IN NORM AND WITH LPS-INDUCED GENERAL INFLAMMATION

A. G. Sysa[1], E. I. Kvasyuk[1], A. Shihad[1,2], M. S. Hassan[2]
[1] Belarusian State University, ISEI BSU, Minsk, Republic of Belarus
[2] University of Al-Qhadisayh, College of Veterinary Medicine, Al Diwaniyah, Iraq

Background. The widespread use of antibiotics has led to the emergence and rapid spread of resistance in microorganisms. Potential antibacterial activity is postulated for modified nucleosides and nucleotides. Along with studying the mechanisms of the antibacterial action of modified nucleosides and nucleotides, it is important to take into account the systemic reactions of the host organism to the introduction of these compounds.

Objective. To characterize changes in diagnostically significant hematological and biochemical blood parameters during systemic inflammation caused by *E. coli* lipopolysaccharide administration to rats and its modulation by modified nucleosides/nucleotides in a model experiment on laboratory animals.

Material and Methods. The study was performed on Wistar male rats. Animals were immunized with *E. coli* lipopolysaccharide intraperitoneally, then 7 days later they were injected with modified nucleotides and nucleosides. The hematological and biochemical status of rats was assessed.

Results. Seven modified nucleosides and nucleotides have been synthesized: fludarabine, fludarabine phosphate, 2-NH2-6-Cl-araPur, ara-C, TTU, cCMP, and ara-CMP. Tests were carried out on laboratory animals with an experimental systemic inflammatory process.

Conclusions. *S*tudied nucleosides and nucleotides increase the severity of nephrotic and hepatobiliary syndromes of the inflammatory process. The cCMP and ara-CMP nucleotides, as well as the TTU nucleoside, had the most pronounced effects.

Keywords: modified nucleosides, endotoxin, anemia, hepatobiliary system, inflammation.

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Introduction

Bacterial resistance to one or more antibiotics is becoming a growing concern. Therefore, it is essential to create new types of antibacterial drugs that might be applied to the treatment of bacterial diseases. This is crucial for treating serious infections, which kills over a million people a year and is exhibiting worrying signs of developing antibiotic resistance [1].

One of the little-studied classes of compounds with potential antibacterial activity are derivatives of nucleic acid components: nucleosides, nucleotides, as well as their modified analogues. Nucleotides and nucleosides, being the main structural units of DNA and RNA, participate in protein biosynthesis, act as cofactors of many biochemical processes, regulate the activity of enzymes of nucleotide metabolism. In this regard, even small modifications of the nucleic base or sugar fragment of the nucleoside can have a significant impact on the recognition and inhibition of the respective enzymes, and thus on its activity as an antipathogen. Nucleic acid analogs and derivatives are currently important elements of anticancer, and antiviral therapy [2, 3]. In addition to being effective against viral and cancer infections, natural nucleosides analogs have recently been found to be effective against the development of *M. tuberculosis* [4], albeit the molecular targets are still completely unknown. Additionally, purine analogs have been demonstrated to stop *Escherichia coli* growth [5].

At the same time, among the representatives of modified nucleosides antibacterial activity was discovered only recently [6], and this area is actively developing [7].

Therefore, the search for new compounds with potential antibacterial activity in a series of modified nucleosides and nucleotides is of fundamental and practical importance.

Objective – to characterize changes in diagnostically significant hematological and biochemical blood parameters during systemic inflammation caused by *Escherichia coli* lipopolysaccharide administration to rats and its modulation by modified nucleosides/nucleotides in a model experiment on laboratory animals.

Material and Methods

The modified nucleosides and nucleotides of the purine and pyrimidine series studied in the work were synthetized as described [8]. Purine nucleoside analogs are represented by compounds halogenated at the nitrogenous base, 2-fluoro-arabinofuranosyladenine (fludarabine) and 2-amino-6-chloro-arabinofuranosylpurine (2-NH_2-6-Cl-araPur). Pyrimidine nucleosides are represented by sugar-modified arabinofura-

nosylcytosine (cytarabine, ara-C), which contains arabinose instead of ribose, and [1-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-4-(1,2,4-triazol-1-yl)]uracil (TTU), which is modified at the carbohydrate fragment (three acetate groups) and the nitrogenous base (triazole in the 4th position) (Figure 1).

To study the changes in blood biochemical marks caused by of *E. coli*, the isolates were tested for their activity to grow in a biofilm [9], briefly in this method, brain heart infusion broth (BHIB) containing tubes were inoculated with the isolated bacteria, incubated at 37 °C for 24 h, then the content of the tubes was poured and drops of crystal violet was added to the tubes with gentle rotation, left for two minutes, then the tubes placed upside down on a filter paper after rinsing with distilled water to remove excess stain.

Hemolytic activity of *E. coli* was tested by cultivation of bacteria on blood agar plates then incubated at 37 °C for 24 h, a clear zone around the colonies, indicating a positive result [10].

Urine isolate with the highest biofilm formation activity and hemolytic activity were selected for LPS extraction as a pathogenic isolate. In brief, 250 ml of the 24h bacterial growth in brain heart infusion broth (BHIB) were centrifuged at 6000 rpm for 20 minutes, the sediment washed with phosphate buffered saline (PBS) twice then subjected to 15 ml of lysis buffer containing Tris HCl, $MgCl_2$, SDS and β-mercaptoethanol, then placed in water bath at 65 °C for 1 hour to solubilize the sediment, then, 1 ml of proteinase K was added to the preparation to remove contaminants proteins, preparation was incubated at 37 °C for 24 h, then LPS was precipitated at –20 °C using 3 M sodium acetate and cold absolute ethanol, after final centrifugation, the pellet was re-suspended in 9 ml of 10 mM Tris-HCl followed by extraction using hot phenol, where 9 ml of phenol at 65 °C was added and mixed vigorously and then was immediately placed in an ice bath, preparation was centrifuged at 6000 rpm for 15 min and the top aqueous layer was taken, and the extraction was repeated again, then the aqueous layers of the extracted LPS were subjected to dialysis for 48 h against distilled water, and the LPS was lyophilized and stored at –20 °C until use [11].

The experiment was performed at the College of Veterinary Medicine of University of Al-Qhadisayh in strict compliance with The European Convention for the Protection of Vertebrate Animals Used for Experiments or for Other Scientific Purposes (Directive2010/63/EU) [12], Institutional animal care and use committee (IACUC) approval № 1047/2 from 20.06.2023. Forty-five adult male Wistar rats of 8-10 weeks age and weights between 160-210 grams were obtained from the Animals House, College of Veterinary Medicine, University of Al-Qhadisayh were kept under standard laboratory condition, they were given standard locally prepared diets and were placed in cages and were acclimatized for a week. Next rats were divided into 9 groups (5 rats each), one group was the control group (was given standard saline solution) and the other 8 groups were the experimental groups. The first experimental group was injected intraperitoneally with only LPS (5 mg\kg BW). Eight others experimental groups were injected with LPS and the synthesized nucleosides\nucleotides. All concentrations of used materials were injected

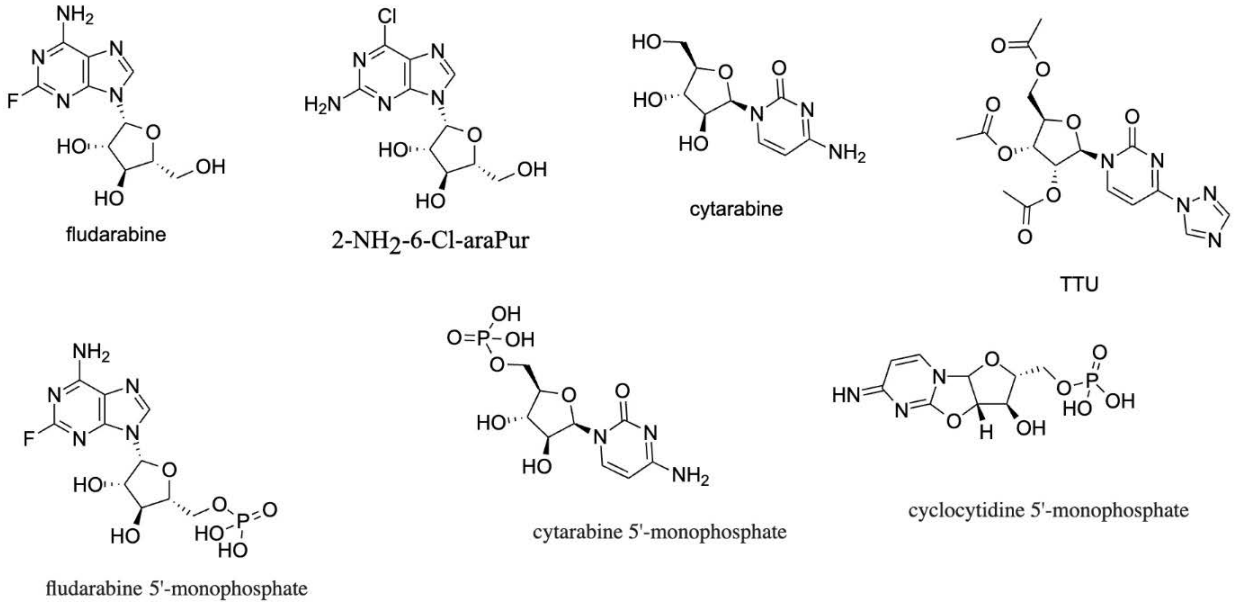

Figure 1 – The structure of the modified nucleosides and nucleotides used in the work

Рисунок 1 – Структурные формулы исследованных модифицированных нуклеозидов и нуклеотидов

with 3 repeated doses 48 h between them, after 7 days of immunization with LPS, the blood was collected using retro orbital blood collection technique and placed in EDTA tubes.

Four clinical and morphological blood parameters were measured on a Celltac α (Japan) hematological analyzer: hemoglobin (HGB) g\dl; hematocrit (HCT) %; leukocytes count (WBC) 103\μl; relative concentration of lymphocytes (LYMP) %.

The study of biochemical parameters of blood serum was performed on a biochemical analyzer of the semi-automatic type BioChemSA (USA). The following parameters were analyzed: blood urea nitrogen (BUN) mg/dl, glucose (GLUC) mg/dl, total protein (TP) g\dl, total bilirubin μmo/l, alanine aminotransferase enzyme activity (ALT) IU/L, aspartate aminotransferase enzyme activity (AST) IU/L.

The data was summarized, analyzed, and presented using the Statistical analysis for Social Science version 23 software program and the difference in mean of quantitative variables between groups was investigated using a one-way ANOVA, which was accompanied by a post hoc Duncan multiple range test.

Results

We used the reference values for Wistar rats in a comparative analysis of hematological study data, but we used the outcomes of control group investigations as the reference [13]. Table 1 shows the dynamics of the parameters of the general blood test of rats (M±m). The administration of bacterial lipopolysaccharide to rats resulted in a significant reduction in hemoglobin content (by 44.7 %) and hematocrit (by 45.6 %) (Table 1), indicating anemia of inflammation that occurs during the development of a pathogenic response.

According to the data in Table 1, the number of erythrocytes and blood hemoglobin in animals that received injections of the studied compounds after 7 days of LPS immunization decreased significantly throughout the entire observation period to 54.3–67.2 % and 46.2–66.2 %, respectively. A slower drop in blood hemoglobin content compared to the number of erythrocytes suggests that anemia has a compensatory nature at first, but the discovered pattern implies a decline in compensatory mechanisms with time.

In terms of white blood cells and the relative concentration of the lymphocyte fraction, the content of leukocytes and the proportion of lymphocytes increased by 71.5 % and 23.8 %, respectively, following administration of bacterial lipopolysaccharide. The administration of modified nucleosides or nucleotides to animals resulted in an increase in symptoms of an acute inflammatory process on the part of leukocytes, as indicated by the results provided in Table 1. The most prominent lymphocytic leukemia was found with the cCMP and ara-CMP nucleotides, as well as the TTU nucleoside (an increase in leukocyte content of 51.9 %, 58.6 %, and 51.9 %, respectively, compared to the LPS-immunized group).

We used the reference values for Wistar rats in a comparative analysis of biochemical blood test data, but we used the findings of investigations of the control groups as the reference [13]. Table 2 shows the dynamics of markers of biochemical blood analysis in rats (M±m).

According to the data in Table 2, signs of impaired renal function in the experimental group rats increased over time, as evidenced by an increase in the content of urea in the blood by 78.9 % 7 days after infection, as well as a more than twofold increase in the content of chlorides (2.2 times). A higher total protein level (68.4 % higher than in the control group) implies an acute infectious process. This idea is supported by a 46.4 % rise in the quantity of glucose in the blood serum, since the body releases hormones to control inflammation during an infection. They have a counter-insulin impact, which means they diminish insulin's efficacy in the body. An increase in the activity of the liver enzymes ALT and AST by 2.3 and 1.3 times is also a marker of dysfunction of the hepatobiliary system, and may also be a consequence of the development of hemolytic anemia.

Table 1 – Hematological status of laboratory rats with experimental systemic inflammation induced by bacterial endotoxin

Таблица 1 – Гематологический статус лабораторных крыс при экспериментальном системном воспалении, индуцированном бактериальным эндотоксином

Groups	HGB (g\dl)	HCT (%)	WBC (103\μl)	LYMP (103\μl)
Control	14.5±0.78	46±0.97	13.09±1.12	3.9±1.4
LPS-treated	8.02±0.87	25±0.76	22.45±0.94	9.01±1.3
LPS + Fludarabine	7.8±0.66	21±0.67	30.1±1.2	11.1±1.0
LPS + 2-NH_2-6-Cl-araPur	9.3±0.72	19±0.96	27.2±0.93	10.5±1.1
LPS + ara-CMP	6.1±0.75	19.4±0.71	35.6±1.1	10.4±0.94
LPS + TTU	6.8±0.85	21.7±0.72	34.1±1.1	9.9±1.1
LPS + Fludarabine phosphate	7.4±0.70	19±0.83	27.8±1.1	10.2±1.1
LPS + araC	5.6±0.81	17.7±0.85	29.3±0.96	9.3±0.99
LPS + cCMP	4.9±0.79	15.1±0.83	33.6±0.85	10.6±0.86

Table 2 – Biochemical status of laboratory rats in experimental systemic inflammation induced by bacterial endotoxin

Таблица 2 – Биохимический статус лабораторных крыс при экспериментальном системном воспалении, индуцированном бактериальным эндотоксином

Groups	AST (IU/L)	ALT (IU/L)	BUN (mg/dl)	GLUC (mg/dl)	TP (g\dl)	Cl (mmol\l)
Control	142±1.1	36±1.4	19±0.78	112.03±0.88	9.5±0.98	103±1.2
LPS-treated	182±0.99	59±1.2	34±0.89	164±1.2	16±0.78	223±1.3
LPS + Fludarabine	189±1.2	67±0.99	43±0.65	171±1.1	23±0.93	227±0.99
LPS + 2-NH_2-6-Cl-araPur	174±0.82	54±1.1	39±0.88	167±1.2	20±0.87	225±1.1
LPS + ara-CMP	192±1.3	72±1.2	45±0.73	179±1.2	27±0.86	233±0.82
LPS + TTU	186±1.1	75±1.1	52±0.71	183±0.98	31±0.96	230±0.92
LPS + Fludarabine phosphate	191±0.89	65±1.0	39±0.73	176±0.83	19.8±0.87	220±1.1
LPS + araC	189±0.92	70±0.97	39±0.86	162±0.90	25±0.78	210±0.98
LPS + cCMP	192±0.97	76±0.84	43±0.81	174±0.86	29±0.97	227±0.94

Following administration of modified nucleosides or nucleotides to animals, symptoms of an acute inflammatory process increased, followed with disruption of the excretory and hepatobiliary systems. The nucleotides cCMP and ara-CMP, as well as the nucleoside TTU, exhibited the most dramatic effects, increasing total protein content by 1.8, 1.7, and 1.9 times, respectively, compared to the LPS-immunized group; and increasing ALT activity by 1.3, 1.2, and 1.3 times, respectively.

Conclusions

A study of the effects of modified 2-fluoro-arabinofuranosyladenine (fludarabine), 2-amino-6-chloro-arabinofuranosylpurine (2-NH_2-6-Cl-ara-Pur), arabinofuranosylcytosine (cytarabine, ara-C), [1-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-4-(1,2,4-triazol-1-yl)]uracil (TTU) nucleosides and 2-fluoro-arabinofuranosyladenine-5 O^2,2'-monophosphate (fludarabine monophosphate), cytarabine-5'-monophosphate (ara-CMP) and O^2,2'-cyclocytidine-5'-monophosphate (cyclocytidine monophosphate, cyclo-CMP) nucleotides, suggests that the modified nucleosides and nucleotides have modulating effect on the systemic inflammatory response.

The results of the research show a significant alteration in the hematological and biochemical patterns in the laboratory animals that were given the test chemicals.

Seven days after systemic administration of *E. coli* lipopolysaccharide, intraperitoneal administration of the investigated nucleosides and nucleotides alters the patterns of the inflammatory response, specifically increasing the severity of nephrotic and hepatobiliary syndromes of the inflammatory process. The most notable effects were produced by the TTU nucleoside, cCMP, and ara-CMP nucleotides.

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ГЕМАТОЛОГИЧЕСКИЙ И БИОХИМИЧЕСКИЙ СТАТУС В НОРМЕ И ПРИ СИСТЕМНОМ ВОСПАЛЕНИИ, ИНДУЦИРОВАННОМ БАКТЕРИАЛЬНЫМ ЭНДОТОКСИНОМ

А. Г. Сыса[1], Е. И. Квасюк[1], А. Шихад[1,2], М. С. Хассан[2]
[1] Белорусский государственный университет,
МГЭИ им. А. Д.Сахарова БГУ, Минск, Республика Беларусь,
[2] Университет Аль-Кадисия, Колледж ветеринарной медицины, Дивания, Ирак

Введение. Широкое применение антибиотиков привело к возникновению и быстрому распространению резистентности у микроорганизмов. Потенциальной антибактериальной активностью обладают модифицированные нуклеозиды и нуклеотиды. Наряду с изучением механизмов их антибактериальной действия важно учитывать системные реакции организма-хозяина на введение этих соединений.

Цель исследования. В модельном эксперименте на лабораторных животных охарактеризовать изменения диагностически значимых гематологических и биохимических показателей крови при системном воспалении, вызванном введением липополисахарида *E. coli*, и его модуляции модифицированными нуклеозидами/нуклеотидами.

Материалы и методы. Исследование выполнено на крысах самцах Wistar. Животных иммунизировали липополисахаридом *E. coli* интраперитонеально, затем спустя 7 дней инъецировали модифицированными нуклеотидами и нуклеозидами. Оценивали гематологический и биохимический статус животных при экспериментальном системном воспалении.

Результаты. Синтезированы семь модифицированных нуклеозидов и нуклеотидов пуринового и пиримидинового ряда: флударабин, флударабина фосфат, 2-NH_2-6-Cl-araPur, ara-C, TTU, cCMP, ara-CMP. Проведены испытания на лабораторных животных с экспериментальным системным воспалительным процессом.

Заключение. Исследованные соединения усиливают выраженность нефротического и гепатобилиарного синдромов воспалительного процесса. Наиболее выраженными эффектами обладали нуклеотиды cCMP и ara-CMP, а также нуклеозид TTU.

Ключевые слова: Модифицированные нуклеозиды, эндотоксин, анемия, гепатобилиарная система, воспаление.

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