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THE EFFECT OF “NUCLEX” AND “METABOL-NORM” ON ACID-BASE BALANCE AND EXPRESSION OF SELECTED GENES IN MOUSE BLOOD

Blood acid-base status is a critical factor in infectious diseases-particularly severe viral infections – and is associated with increased morbidity and mortality. Current therapeutic approaches to correcting acid-base status are limited by a reliance on respiratory compensation and the risk of CO₂ overload. Therefore, the development of new agents capable of restoring buffering capacity without increasing the respiratory load is of significant importance. The aim of the study was to evaluate the effects of the preparations “Nuclex” (a complex of protonated oligoribonucleotides with D-mannitol) and “Metabol-norm” on acid-base status parameters and gene expression in the blood of mice kept under uncontrolled wartime conditions. **Methods.** The study was conducted in vivo using BALB/c mice. Blood gas parameters (pH, pCO₂, HCO₃⁻, base excess (BE)) were analyzed, as well as the expression levels of transcription factors (c-Myc, Klf, Sox2, Rela, Nfkb) and cytokine genes (Ifna2, Ifn1β, Ifnγ, Il6, Tnf) using RT-qPCR. **Results.** Administration of the drug “Nuclex” resulted in a significant increase in pH, restoration of bicarbonate (HCO₃⁻) levels, and a reduction in base deficit (BE), indicating effective correction of blood acid-base parameters without lowering pCO₂. In contrast, the use of “Metabol-norm” alone did not ensure complete normalization of these parameters. Combined therapy demonstrated the most pronounced effect. At the molecular level, “Nuclex” reduced c-Myc and Rela expression, stabilized Nfkb levels, and decreased variability, indicating a normalization of the cellular inflammatory state. Furthermore, “Nuclex” selectively increased Ifnγ expression without affecting Ifna2 or Ifn1β, indicating a shift towards a controlled Th1-type immune response. **Conclusions.** The obtained results support the concept that protonated oligoribonucleotides act as non-bicarbonate buffering agents capable of binding H⁺ ions, replenishing bicarbonate reserves, and stabilizing acid-base homeostasis.

Keywords: Nuclex, Metabol-norm, blood gas parameters, transcription factors, cytokine genes.

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Introduction

High-consequence viral infections, such as coronavirus (SARS-CoV-2), Ebola virus (EBOV), Marburg virus (MARV), Lassa virus (LASV), Crimean-Congo hemorrhagic fever (CCHF), and Nipah virus (NiV), represent some of the most severe infectious threats to humanity [1–6]. These pathogens are characterized by high mortality rates, severe hemorrhagic or neurorespiratory syndromes, and profound disturbances in blood microcirculation. A universal hallmark of severe viral hemorrhagic fevers (VHF) is metabolic acidosis. According to WHO and CDC clinical protocols, the levels of pH, HCO_3^- , base excess (BE), lactate, and pCO_2 are the key markers of severity, disease progression, and prognosis for these infections [3–5]. Acid-base imbalance in these infections is complex and multifactorial, reflecting dysfunction in the cardiovascular, respiratory, renal, and immune systems.

Characteristic clinical manifestations of EBOV, MARV, and CCHF infections include endothelial damage, increased vascular permeability, and the development of capillary leak syndrome, which have been extensively described in the literature [1, 2, 6–8]. Consequently, this damage leads to hypoperfusion and tissue hypoxia, resulting in anaerobic glycolysis and lactate accumulation. An increase in lactate levels above 4–5 mmol/L is an independent predictor of mortality and is accompanied by a decrease in pH and HCO_3^- [12, 13]. In cases of infection, EBOV and LASV can cause significant fluid loss due to severe diarrhea, leading to bicarbonate depletion and the development of metabolic acidosis [3]. In patients infected with EBOV and Lassa, renal tubular damage and acute kidney injury (AKI) have been described, leading to impaired clearance of organic acids and reduced HCO_3^- regeneration [4, 5]. Coronaviruses such as SARS-CoV-2, as well as NiV, EBOV, and MARV, can cause acute respiratory distress syndrome (ARDS), which is characterized by rapid, severe dyspnea and fluid accumulation in the alveoli [9–11]. This condition triggers pulmonary hyperven-

tilation, characterized by very rapid breathing, which eliminates more carbon dioxide (CO_2) from the body than is produced. In the body of a healthy person, CO_2 helps compensate for acidosis, whereas during illness, its concentration drops sharply and becomes depleted to a critically low level. Consequently, during acidosis, pH and HCO_3^- decrease, and BE becomes negative, resulting in impaired myocardial contractility, enzyme function, ion transport, blood coagulation, and energy metabolism. Similar symptoms have been described in severe forms of influenza, such as the "Spanish flu" or avian influenza. Therefore, the normalization of buffer capacity is one of the most critical components of therapy for severe viral infections.

Pharmacological correction of acidosis in the context of severe viral infections has several limitations, which can result in elevated CO_2 levels, increased workload on the respiratory system, and overall clinical deterioration of the patient [12]. The efficacy of such treatment is also reduced in the presence of comorbidities, such as hepatic hypoperfusion, which is characteristic of VHF. Thus, there is an acute need for drugs capable of increasing buffer capacity without causing an additional CO_2 burden and without relying on ventilatory compensation [13, 14].

"Nuclex" is a complex of short oligoribonucleotides (2–5 nucleotides) combined with mannitol. The oligoribonucleotides contain phosphate groups, which are key components of the non-bicarbonate buffer system: $\text{H}_2\text{PO}_4^- \rightleftharpoons \text{HPO}_4^{2-} + \text{H}^+$. This equilibrium operates within a pH range of 6.8–7.4, making phosphates highly effective under acidotic conditions. Mannitol, acting as a polyol, creates a dense hydration shell that increases proton mobility and improves the distribution of the acid load. Since Nuclex is a composition of oligoribonucleotides, its structural-dynamic properties depend largely on the RNA hydration shell, the state of which determines the RNA's conformational mobility. At the same time, surface-bound water is characterized by slowed diffusion and longer-lived hydrogen bonds, which can influence the accessibility of oligoribonucleotide

functional groups during molecular interactions [15–18]. Together, two components of Nuclex can bind H^+ , reduce acidity, shift the equilibrium between CO_2 and HCO_3^- , and restore the bicarbonate pool without increasing pCO_2 . Our studies have demonstrated that the Nuclex drug, represented by oligoribonucleotides in complex with D-mannitol, blocks viral adhesion [19, 20], alters the charge and conformation of viral proteins, activates the interferon pathway, and stabilizes the cellular microenvironment, including pH. This makes “Nuclex” a unique therapeutic agent with dual antiviral and metabolic action [21–23].

The composite agent “Metabol-norm” is a complex of metabolically balanced compounds. Its composition includes sodium bicarbonate, citric acid and its salts (sodium and potassium citrate), as well as magnesium, zinc, and manganese compounds, among others. The daily dose of “Metabol-norm” for humans and animals is established at a rate of 0.1 g per kg of body weight (under acidotic conditions), and for prophylactic purposes, at a rate of 0.05 g per kg of body weight. “Metabol-norm” promotes enhanced hepatocyte regeneration, increases their glycogen and ribonucleic acid content, boosts the activity of several enzymes, and reduces the severity of dystrophic manifestations. It also improves capillary-tissue diffusion and tissue oxygen utilization, normalizes the acid-base state, exerts a mineralizing and anabolic effect on bone tissue, accelerates growth processes, stimulates blood regeneration in anemias and the regeneration of damaged tissues, expedites bone fracture healing, and decreases blood glucose and ketone body levels [24].

The aim of this study is to experimentally evaluate the effects of “Nuclex”, “Metabol-norm”, and their combination on the correction of pH, HCO_3^- , BE, and other parameters of the body’s acid-base state. Furthermore, it seeks to identify the systemic effects of these drugs on the gene expression of transcription factors and cytokines using correlation analysis, thereby establishing an integral foundation for the application of “Nuclex” in BSL-3/4 class infections.

Materials and Methods

Experimental animals

Adult male BALB/c mice weighing 30 g were used; they were housed under standard vivarium conditions with ad libitum access to food and water. The experiments were conducted in Kyiv under conditions of active military operations in Ukraine. During the experimental period, the animals were kept in conditions of prolonged external stress associated with the wartime situation. The vivarium was repeatedly subjected to high-intensity noise, vibrations, explosions, and external destabilizing factors capable of sustaining neuroendocrine states in the laboratory animals.

Ethics statement. All procedures involving animals were reviewed and approved by the Bioethics Committee of the IMBG NAS of Ukraine (protocol/permit No. 49, dated 19 February 2026) and conducted in accordance with the Law of Ukraine “On Protection of Animals from Cruelty”, the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS No. 123), ARRIVE guidelines, and international principles of humane treatment of laboratory animals.

Experimental model of acid-base disorders

Under the described conditions, acid-base disorders were observed in mice, characterized by a decreased blood pH, reduced bicarbonate concentration (HCO_3^-) and increased base excess (BE). Given the known effects of prolonged stress, intense acoustic stimuli, explosion hazards, and chronic activation of the neuroendocrine system on energy metabolism, glycolysis, lactate production, and the body’s buffer systems, the identified physiological state was considered a model for stress-induced acid-base disorder in a military setting [25, 26].

The study was conducted using an *in vivo* experimental model to assess blood acid-base balance in male BALB/c mice. The animals, aged 3–3.5 months and weighing approximately 30 g, were monitored

over 11-day period. The drug "Nuclex" was administered orally at doses of 0.15 mg/g and 0.07 mg/g of body weight. Similarly, "Metabol-norm" was administered at a dose of 1.25 mg/g of body weight. The animals were divided into five experimental groups, with each group consisting of 6 or 7 male BALB/c mice, aged 3—3.5 months:

Experimental groups

The animals were randomized into the following groups:

1. Ctrl — stressed untreated animals maintained under the same uncontrolled wartime environmental conditions and receiving no study treatment.
2. Nuc07 — animals that were in a war-associated stressful environment and received the drug Nuclex at a dose of 0.07 mg/g of body weight.
3. Nuc15 — animals that were in a war-associated stressful environment and received the drug Nuclex at a dose of 0.15 mg/g of body weight.
4. Met — animals that were in a war-associated stressful environment and received the drug Metabol-norm.
5. Comb — animals that received a combined administration of Nuclex and Metabol-norm.

At the end of the experiment, the animals were killed by decapitation. Terminal mixed blood released during decapitation was collected into open Eppendorf tubes containing 4% sodium citrate and analyzed using an analyzer (ABL90 Flex Plus, Czech Republic) after 2 hours. Because collection was not performed anaerobically at a defined arterial or venous site, contact with ambient air and mixed arterial-venous origin could have affected pO_2 and, to a lesser extent, pCO_2 and pH. Consequently, pO_2 was treated as descriptive only and was not used for physiological or mechanistic interpretation. HCO_3^- and BE were analyzer-derived parameters and were not considered independent direct biochemical measurements.

Real-time (RT)-qPCR analysis

Peripheral blood mononuclear cells (PBMCs) were extracted from the buffy coat by centrifugation of

the whole blood sample at 2000 rpm for 15 min at +4 °C. TRI-Reagent (Zymo Research, USA) was added to extracted PBMCs (1 : 3) to prevent RNA degradation and mixed well using Vortex. The PBMCs samples were stored immediately at –80 °C. Total RNA was extracted from mouse PBMCs using the Direct-zol RNA Miniprep Plus kit (Zymo Research, USA) according to the manufacturer's protocol with minor modifications [27]. The quality of the isolated RNA was analyzed using a Microchip Electrophoresis System MCE-202/MultiNA (SHIMADZU, Germany) with the RNA reagent kit for MultiNA (SHIMADZU, Germany) and SYBR Green II RNA dye (Life Technologies, USA). RNA quantity was determined spectrometrically, and RNA purity was assessed by the 260/280 nm absorbance ratio using a MaestroNano Pro Micro-Volume MN913 spectrophotometer (MAESTROGEN, Taiwan). cDNA was synthesized from each total RNA sample using the Maxima First Strand cDNA Synthesis Kit for RT-qPCR (Thermo Scientific, USA). Reverse transcription was performed using 1 µg of total RNA per sample; the protocol included incubation for 10 minutes at 25 °C, followed by 120 minutes at 50 °C. The reaction was terminated by heating at 85 °C for 5 minutes.

The mRNA level of the studied genes was quantified using a CFX96 Real-Time PCR Detection System (BIO-RAD, Singapore) with HOT FIREPol EvaGreen qPCR Mix Plus (Solis BioDyne, Estonia). The cDNA was amplified using gene-specific primers (Table 1). Primer sequences were synthesized by Invitrogen (USA). Mean fold change values were determined using the $2^{\Delta\Delta Ct}$ method [28]. The mRNA level of all studied genes was normalized to *Tbp* mRNA as a reference control, with *Tbp* mRNA expression set to 100 expression units.

Statistical analysis was performed using the Kruskal–Wallis test to assess overall differences among groups. When appropriate, pairwise comparisons were performed using two-sided Mann–Whitney U tests. Data are presented as median and interquartile range (IQR). The animal was considered the biological experimental unit. Statistical significance was defined as an adjusted

value below 0.05. Given the small group sizes and exploratory design, statistical findings were interpreted together with effect direction and variability. pO_2 was excluded from inferential analysis because of the preanalytical limitations of blood collection.

Results

General changes in acid-base status. Analysis of mixed blood samples collected at the end of the experiment revealed intergroup differences in acid-base parameters. In the group of animals subjected

Table 1. Primer sequences used for gene expression profiling

Gene	Product	Primer's sequences (5'→3')	Product (bp)	Source
<i>Sox-2</i>	SOX-2	F CAG CTC GCA GAC CTA CAT GA R CTC GGA CTT GAC CAC AGA GC	109	Designed by the Primer-BLAST
<i>Klf</i>	KLF	F CTG AAC AGC AGG GAC TGT CA R GAG GGG ACT TGT GAC TGC AT	113	Designed by the Primer-BLAST
<i>c-Myc</i>	MYC	F ACG TCT TGG AAC GTC AGA GG R GCC TTT TCG TTG TTT TCC AA	91	Designed by the Primer-BLAST
<i>Ifnα2</i>	IFN- α	F CTT ACT CAG CAG ACC TTG AAC C R CTG CTG CAT CAG ACA GGT TT	132	[29]
<i>Ifnβ1</i>	IFN- β	F GAT GCT CCA GAA TGT CTT TCT TGT R CGA ATG ATG AGA AAG TTC CTG AAG A	288	[29]
<i>Ifnγ</i>	IFN- γ	F AAC TGG CAA AAG GAT GGT GA R GTT GTT GAC CTC AAA CTT GGC	204	[29]
<i>Il6</i>	IL-6	F CTA CCA AAC TGG ATA TAA TCA GGA AAT R TCT TTT ACC TCT TGG TTG AAG ATA TGA	180	[29]
<i>Tnf</i>	TNF	F AAA GGG ATG AGA AGT TCC CAA AT R ACT TGG TGG TTT GCT ACG AC	127	[29]
<i>Nfκbα</i>	NF- κ B α	F GAG ACT CGT TCC TGC ACT TG R AAG TGG AGT GGA GTC TGC TG	130	[29]
<i>Rela</i>	NF- κ B3	F GTACTTGCCAGACACAGATGAT R GTTCAGTTGGTCCATTGAAAGG	110	Designed by the Primer-BLAST
<i>Tbp</i>	TBP	F CTA CCG TGA ATC TTG GCT GTA AAC R AAT CAA CGC AGT TGT CCG TGG C	131	[30]

Table 2. Descriptive acid-base and blood-gas parameters in terminal mixed blood (median [Q1—Q3])

Group	pH	pCO ₂ (mm Hg)	pO ₂ (mm Hg)	BE (mmol/L)	HCO ₃ ⁻ (mmol/L)
Ctrl (n = 6)*	7.16 ± 0.10	27.2 ± 6.8	86.2 ± 50.9	-17.6 ± 5.4	10.3 ± 4.4
Met (n = 6)	7.14 ± 0.10	24.6 ± 3.6	68.0 ± 18.0	-19.0 ± 4.4	8.1 ± 2.0
Nuc15 (n = 7)	7.27 ± 0.08	32.1 ± 5.3	53.6 ± 15.8	-10.3 ± 5.0	15.2 ± 4.4
Nuc07 (n = 6)	7.27 ± 0.05	30.7 ± 6.7	72.3 ± 8.8	-8.4 ± 2.1	16.1 ± 1.2
Comb (n = 6)	7.32 ± 0.06	22.2 ± 7.7	135.0 ± 47.2	-12.0 ± 3.7	11.9 ± 4.1

* Ctrl denotes the stressed untreated group and is not a physiologically normal control. pO_2 values in Table 2 are reported descriptively only and were excluded from inferential and mechanistic interpretation because blood was not collected anaerobically. Values below 0.05 in Table 3 indicate exploratory between-group differences after the stated multiple-comparison procedure.

to stress but receiving no treatment (Ctrl), the values were as follows: pH — 7.16 ± 0.10 ; HCO_3^- — 10.3 ± 4.4 mmol/L; BE — -17.6 ± 5.4 mmol/L (Table 2). This pattern indicated acidemia with a metabolic component. Compared to the Ctrl group, the Nuc15, Nuc07, and Comb groups exhibited higher pH values and less negative BE values, while the Nuc15 and Nuc07 groups also showed higher HCO_3^- levels. Administration of the Metabol-norm preparation alone did not result in a comparable improvement in these parameters.

Effect of the drugs on blood pH

The comparison of acid-base balance (ABL) parameters between the five experimental groups (Ctrl, Met, Nuc15, Nuc07, Comb), presented in Fig. 1, indicates the median, interquartile range, variability and potential dispersion of values.

For pH (Fig. 1a), the stressed untreated Ctrl and Met groups showed lower central values and greater dispersion than the Nuclex-treated groups. The higher pH values in the Nuc07, Nuc15, and Comb groups represent differences relative to the stressed untreated group only; because an unstressed healthy control was not included, they cannot be interpreted as complete physiological normalization.

For the parameter HCO_3^- (Fig. 1), low and critically low values were found in the Ctrl group. These low values indicate a bicarbonate deficiency due to the development of metabolic acidosis. The Nuc15 and Nuc07 groups showed significantly higher HCO_3^- values. They normalized due to the restoration of the alkaline reserve. The HCO_3^- level reached its maximum in the Nuc07 group at 16.1 ± 1.2 , and in the Nuc15 group — 15.2 ± 4.4 . These data indicate an enhanced regeneration of bicarbonate under the influence of Nuclex. Compared with the Ctrl group, which had a HCO_3^- value of 10.3 mmol/L, the increase in the concentration of HCO_3^- in the blood of mice was 55% higher for the Nuc07 group, 48% for the Nuc15 group and 15% for the Comb group.

Regarding the BE parameter (base excess), it is more negative in the Ctrl and Met groups, indicat-

ing a deficiency of bases during acidosis (Fig. 1). This parameter reflects the lack of alkaline compounds, mainly bicarbonates, necessary to neutralize excess acids. A more negative BE is a key marker of metabolic acidosis. The increase in the BE index to more positive values in the Nuc15 and Nuc07 groups indicates an increase in the total buffer capacity, due not only to the HCO_3^- component. Negative BE is a sign of metabolic acidosis. It was the most negative in the control group (-17.6) and the Met group (-19.0). Concurrently, the administration of Nuclex increased the BE value to -10.3 in the Nuc15 group and to -8.4 in the Nuc07 group. Therefore, the Nuc07 group demonstrated the most comprehensive correction of the base deficit (Fig. 1).

Mean pCO_2 values were 27.2 ± 6.8 mmHg in Ctrl, 24.6 ± 3.6 mmHg in Met, 32.1 ± 5.3 mmHg in Nuc15, 30.7 ± 6.7 mmHg in Nuc07, and 22.2 ± 7.7 mmHg in Comb (Fig. 1D). Lower pCO_2 may be compatible with respiratory compensation, but ventilation and respiratory rate were not measured, and the collection procedure could have affected this parameter. pO_2 showed marked variability, particularly in Ctrl and Comb, and was not interpreted because it is highly sensitive to contact with ambient air. The available data do not support conclusions regarding respiratory distress, suffocation, or a

Table 3. Exploratory group comparisons for acid-base parameters

Comparison	pH	HCO_3^-	BE	pCO_2
Ctrl vs Met	n.s.	n.s.	n.s.	n.s.
Ctrl vs Nuc15	0.015	0.009	0.020	0.041
Ctrl vs Nuc07	0.008	0.005	0.010	0.033
Ctrl vs Comb	0.004	0.049	0.015	n.s.
Met vs Nuc15	0.020	0.010	0.017	0.040
Met vs Nuc07	0.015	0.008	0.013	0.046
Met vs Comb	0.004	0.044	0.007	n.s.
Nuc15 vs Nuc07	n.s.	n.s.	n.s.	n.s.
Nuc15 vs Comb	n.s.	0.049	n.s.	0.027
Nuc07 vs Comb	0.040	0.015	0.020	0.016

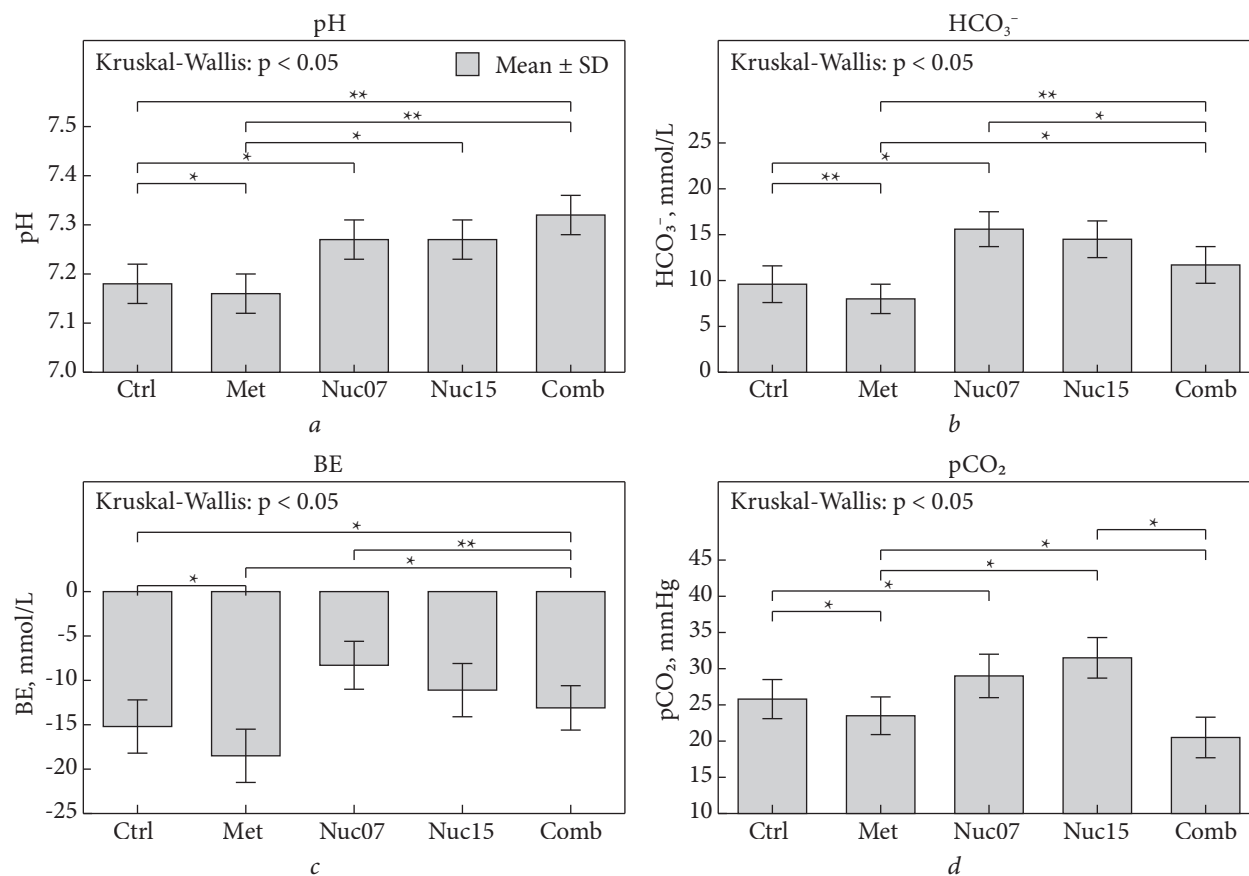


Fig. 1. Acid-base parameters in terminal mixed blood across experimental groups. Panel A: pH; Panel B: analyzer-derived bicarbonate (HCO_3^-); Panel C: base excess (BE); Panel D: pCO_2 . Bars show mean $\pm$ SD, and open circles show individual observations. Ctrl denotes the stressed untreated group. The figure does not establish normalization to a healthy physiological reference

purely metabolic mechanism of treatment-associated change.

Taken together, pH, analyzer-derived HCO_3^- , and BE differed between the stressed untreated group and several Nuclex-treated groups. However, the mathematical interdependence of these parameters, the non-anaerobic collection procedure, and the absence of metabolic, renal, and ventilation measurements prevent attribution of these differences to a specific buffering mechanism.

The revised analysis therefore focuses on individual acid-base parameters. pO_2 was not used to classify the experimental groups or to infer treatment effects, and no PCA-based physiological classification is presented.

The correlation heatmap showed a strong positive relationship between analyzer-derived HCO_3^- and BE (Fig. 2). Because both parameters are mathematically related to the measured blood-gas variables, this correlation is expected and should not be regarded as independent confirmation of physiological validity.

The observed correlations are descriptive and do not establish that the treatment acted through a metabolic rather than respiratory mechanism. In particular, the association among pH, HCO_3^- , and BE partly reflects the derivation of HCO_3^- and BE from the blood-gas measurements. pO_2 was excluded from physiological interpretation because of the sampling limitations described above.

Effect of the drugs on the gene expression of transcription factors in blood during acidosis

The experimental results examining the changes in *Klf* gene expression during murine blood acidosis, presented as a box plot (Fig. 3), indicate that an increased level of the *Klf* gene expression is observed in the Met group compared to the control. In the Nuc07 group, treatment with the lowest dose of Nuclex does not lead to significant changes in the *Klf* expression compared to the control. Conversely, the lowest level of the *Klf* expression is observed in the Nuc15 group, which received a higher concentration of Nuclex, and in the combined Comb group.

Fig. 3 presents the changes in the *c-Myc* gene expression during blood acidosis under the action of the drugs. It is shown that the Met group exhibits a very high increase in the *c-Myc* expression (almost

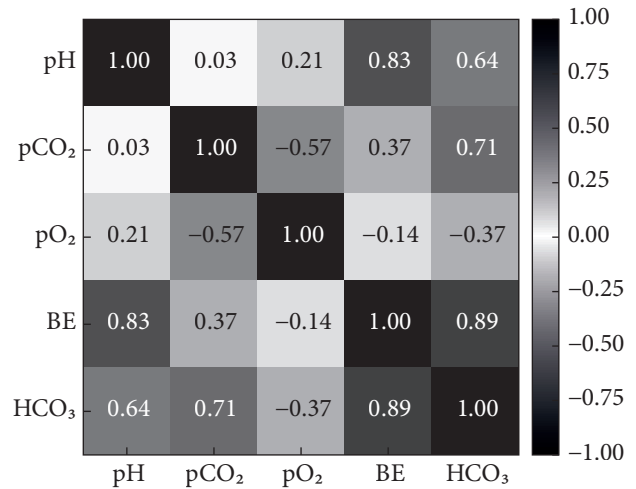


Fig. 2. Correlation matrix for the measured and analyzer-derived acid-base parameters. Color intensity represents the direction and magnitude of the correlation. Correlations involving HCO₃⁻ and BE should be interpreted in view of their mathematical interdependence

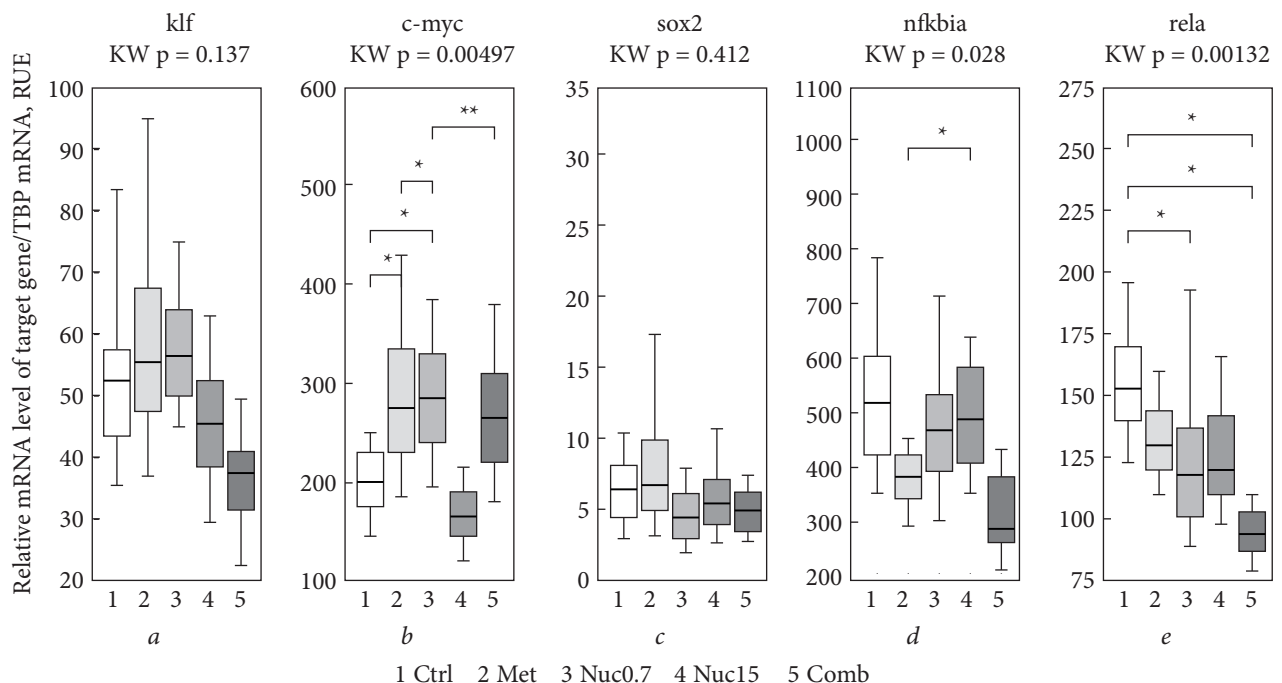


Fig. 3. Relative mRNA expression of *Klf*, *c-Myc*, *Sox2*, *Nfkb1a* and *Rela* across experimental groups (Ctrl, Met, Nuc0.7, Nuc15, Comb). Boxes show median and interquartile range; whiskers indicate data range excluding plotted individual observations. Open circles show individual biological/technical measurements from the transcribed dataset. Kruskal-Wallis p-values are shown in each panel. Pairwise comparisons were performed using Mann-Whitney U tests followed by Benjamini-Hochberg FDR correction within each gene. * $q < 0.05$; ** $q < 0.01$

430). Meanwhile, in the groups of mice treated with different concentrations of Nuclex (Nuc07 and Nuc15), the *c-Myc* expression decreases by a factor of 2–4. Combination therapy yields the lowest level of the *c-Myc* expression among the acidosis treatment groups. The experimental results clearly demonstrate that in the control and Met groups, acidosis leads to a glycolytic burst (*c-Myc* is strongly upregulated). At the same time, Nuclex inhibits the *c-Myc* expression in the Nuc07/Nuc15 and Comb groups, where the best metabolic compensation for acidosis is observed. This is one of the most compelling markers of the positive effect of the drug Nuclex on the progression of acidosis in mice.

The box plot illustrating changes in the *Sox2* gene expression during blood acidosis under the action of the drugs (Fig. 3) indicates a massive dispersion of expression values for this gene in the Met group. Simultaneously, in the Nuc07/Nuc15 groups, these values are lower than those of the Ctrl group. In the Met group and the Comb group, the *Sox2* expression stabilizes, and its variability decreases. Thus, under the influence of acidosis, the *Sox2* gene expression in the blood is highly unstable; however, the drug Nuclex reduces its variability, equalizes the regulatory state of the cells, and partially normalizes its transcriptional profile.

The expression level of the *Nfkb* gene during blood acidosis under the action of the drugs is presented in a box plot (Fig. 3). It is shown that the *Nfkb* expression level in the Met group fluctuates but is generally lower than in the control. At the same time, an upregulation of the *Nfkb* expression is observed in the Nuc07/Nuc15 groups, while the combined group exhibits stable, elevated levels of the *Nfkb*. This may indicate that the drug Nuclex downregulates NF- κ B expression by upregulating the *Nfkb* gene, a natural inhibitor of NF- κ B.

As seen in Fig. 3, the expression level of the *Rela* gene during blood acidosis under the action of the drugs is significantly reduced in the Nuc07/Nuc15 groups, with the combination therapy showing the lowest values. Thus, this is key evidence that the

drug Nuclex, which is based on protonated oligonucleotides, specifically targets the NF- κ B axis, which is sensitive to pH and intracellular proton load. These results support the hypothesis that Nuclex acts as a proton regulator of inflammation, accompanied by a decrease in the expression of the protonation-dependent transcription factor NF- κ B, ultimately leading to the normalization of cellular cytokine and transcriptional profiles.

Effect of the drugs on cytokine gene expression in murine blood during acidosis

As seen from Fig. 4, the expression levels of the *Ifna2* gene in the control group vary from low (~3.5) to moderate (~15) values. In the Nuc07/Nuc15 and Comb groups, these values are close to the control.

In contrast, the *Ifna2* expression levels in the Met group are generally higher, but due to the wide variability in the control, the difference is marginal. Thus, no pair of groups shows a significant difference. Therefore, the *Ifna2* gene, which encodes a type I interferon, does not respond to acidosis or the administration of Metabol-norm or Nuclex. Even though the Met group shows an upward trend in the *Ifna2* expression, it is not statistically confirmed. Type I interferons, including IFN- α , are typically involved in the virus-dependent interferon pathway rather than metabolic acidosis; therefore, its stability is expected.

The expression levels of *Ifnb1* in the control, as seen from Fig. 3, exhibit low values (~0.1–1.2), similar to the Met group, which shows a comparable range with a slightly higher maximum (~2.0), as well as the Nuc07, Nuc15, and Comb groups, which fall within the 0.5–2.3 range. No pair achieves FDR significance. The p-FDR values across all groups are approximately 0.8–1. Consequently, the *Ifnb1* gene, which also encodes a type I interferon, does not demonstrate significant sensitivity to acidosis. The intra-group noise level is very similar, and inter-group shifts are minimal. This indicates that type I interferon genes do not

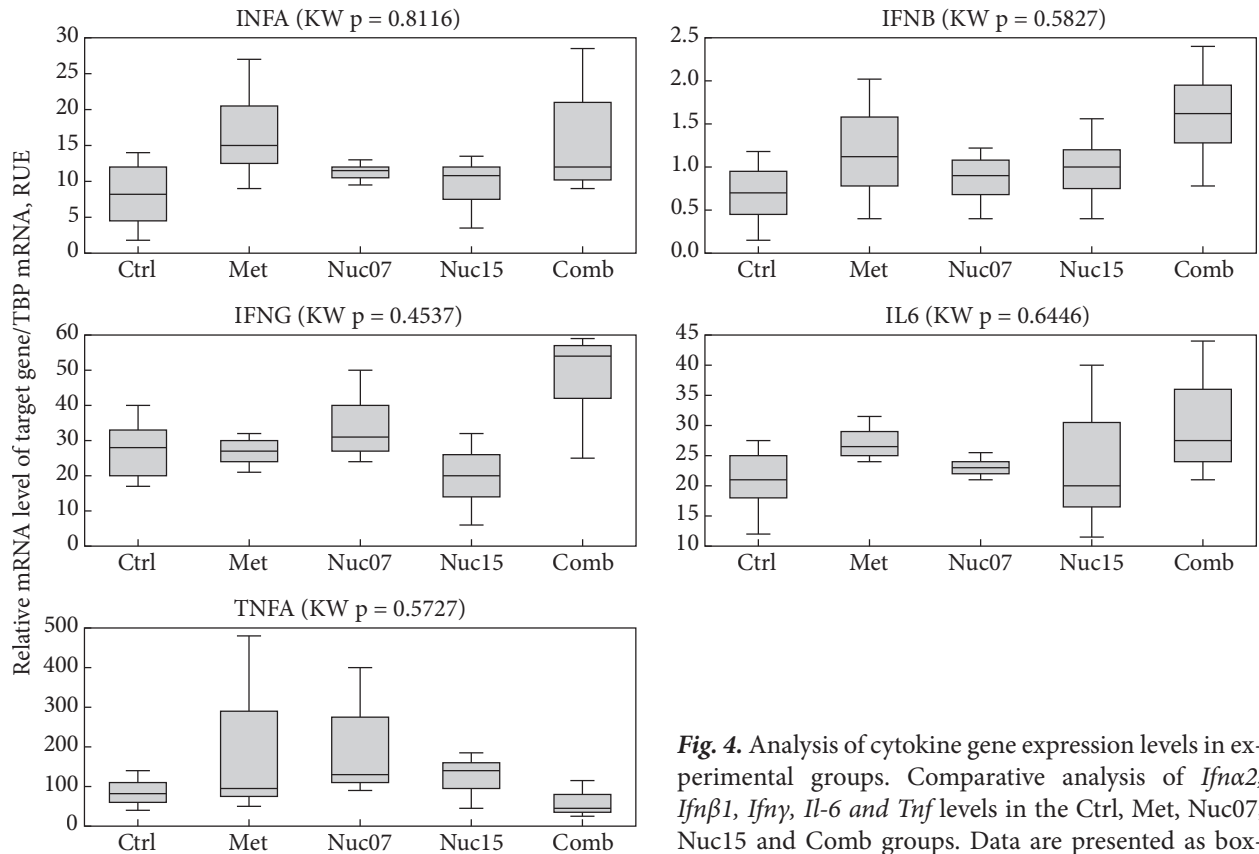


Fig. 4. Analysis of cytokine gene expression levels in experimental groups. Comparative analysis of *Ifna2*, *Ifnb1*, *Ifny*, *Il-6* and *Tnf* levels in the Ctrl, Met, Nuc07, Nuc15 and Comb groups. Data are presented as box-plot diagrams with individual values shown for each

biological sample. The central line indicates the median, boxes represent the interquartile range, and whiskers indicate the data range. Overall differences among experimental groups were assessed using the Kruskal-Wallis test. Pairwise comparisons between groups were performed using the Mann-Whitney U test. Corresponding p-values are provided in the statistical results table

respond to the studied drugs in this model, given the absence of a viral infection.

Effect of the drugs on the *Ifny* gene expression in murine blood during acidosis

As shown in relatively low *Ifny* expression values (4–40) are observed in the control compared to the other groups. In the Met group, it is somewhat higher than the control (24–31); it is slightly higher in the Nuc07 group, reaching a significantly higher peak (up to 50); and the Comb group exhibits the highest *Ifny* expression values among all

groups (56–59). The Nuc15 group, based on its metrics, is closer to the control (12–32). Statistical analysis indicates that the difference between the Ctrl group and the Comb group is significant or marginally significant (frequently, FDR is substantially below 0.1). The difference between the Met and Comb groups is significant (Comb >> Met); it is also substantial between the Nuc15 and Comb groups, while the difference between the Ctrl and Nuc07 groups may be bordering on significance. The difference between the Met and Nuc groups is also frequently distinct. It is known that IFN-γ is the only interferon that genuinely alters during acidosis and its correction. As the experimental results

demonstrate, the combined therapy of Nuclex + Metabol-norm sharply enhances the Th1-type immune response (*Ifn γ*). This may signify a transition from “chaotic” acidotic inflammation to a controlled Th1 immune response. Furthermore, Nuclex 0.15 mg/g produces a strong *Ifn γ* peak, but the combination of Nuclex and Metabol-norm is the most potent.

As can be seen from the graphs in Fig. 4, the *Il6* gene expression levels remained relatively stable between groups and were characterized by only moderate biological variability. Intermediate levels of the *Il6* gene expression were determined in the Ctrl group. Similar values were observed in the Met and Nuc07 groups. The Nuc15 and Comb groups were characterized by a wider deviation of values, including individual samples with increased levels of *Il6*. At the same time, no clear trend towards pronounced activation or inhibition of the *Il6* production was detected, indicating the absence of a strong systemic pro-inflammatory response.

The *Tnf* gene showed the greatest variability in expression among all cytokines studied. Moderate levels of *Tnf* expression were observed in the Ctrl group, while a single sample with sharply increased expression was found in the Met group, which caused a significant deviation of the indicator. Increased values of *Tnf* gene expression were also recorded in the Nuc07 group, mainly due to one high observation. In contrast, the Nuc15 group showed intermediate levels of *Tnf* expression with significant variability. The Comb group was characterized by relatively lower and more homogeneous *Tnf* expression values compared to several other experimental groups. Despite the pronounced individual variability, the overall *Tnf* expression profile did not confirm a clear increase in systemic inflammatory activation due to the studied effects.

In general, the Kruskal-Wallis test was used to assess global intergroup differences, followed by pairwise comparisons using the Mann-Whitney U test. The cytokine profile obtained indicates that the use of Nuclex and the combined effect was more associated with changes in interferon-dependent immune signaling than with the acti-

vation of classical pro-inflammatory cytokine pathways.

Discussion

The results obtained indicate that Nuclex leads to changes in the expression of key transcription factors, genes of innate immunity and compensated blood acid-base parameters in the blood of mice. This indicates a pH-sensitive effect of protonated nucleotides on the acid-base balance of blood and cells. It is known that Nuclex is a complex of protonated ribonucleotides and D-mannitol, the mechanism of action of which is mediated through the regulation and modification of transcriptional and cytokine signaling networks in peripheral blood cells [29].

Fig. 5 illustrates the proposed mechanism of action of Nuclex on the clinical manifestations of blood acid-base parameters. Namely, an increase in H^+ levels and a decrease in HCO_3^- and BE levels, which ultimately leads to normalization of the CO_2/HCO_3^- balance. It demonstrates that the phosphate groups of Nuclex form an additional non-bicarbonate buffer that binds H^+ in the critical pH range. Mannitol, a component of Nuclex, further reduces local acidity by enhancing hydration in the water-polyol-phosphate group system. The reduction of free H^+ shifts the blood buffering response towards HCO_3^- regeneration and improved energy expenditure. Thus, Nuclex helps to normalize blood pH without simultaneously reducing pCO_2 . It thus provides protection against a very harmful load on the body's ventilation. Thus, Fig. 5 supports the concept that Nuclex functions as a non-bicarbonate buffer and regulator of the hydration microenvironment. It stimulates the restoration of HCO_3^- and BE and normalization of pH, avoiding respiratory compensation.

Changes in acid-base status in this model manifest as a decrease in pH, a reduction in bicarbonate concentration, and a base deficit. These physiological disorders coincide with a significant increase in the expression of the *c-Myc* gene. It is known that this gene was previously described as a mar-

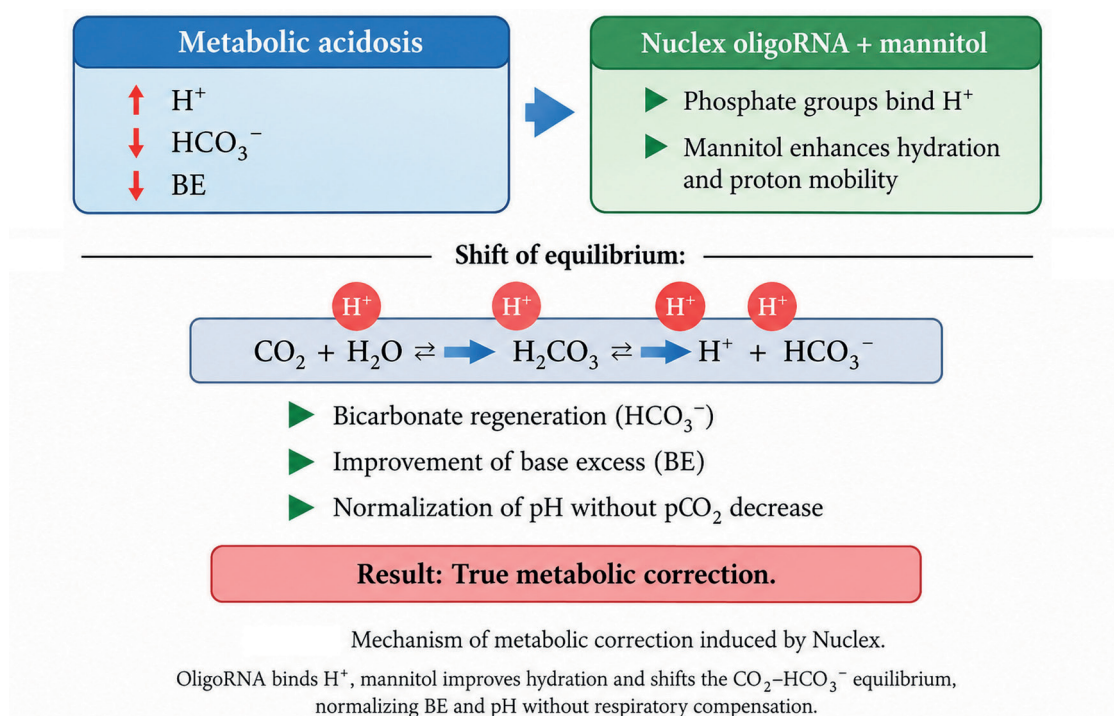


Fig. 5. The proposed mechanism of action of Nuclex on the clinical manifestations of metabolic acidosis

ker of the transition of T cells and monocytes to glycolytic metabolism under stress conditions [31]. At the same time, an increase in the expression of the *Rela* (NF- κ B p65) and *Tnf* genes was observed, which corresponds to the known phenomenon of direct activation of the NF- κ B gene with an increase in proton load [32, 33]. Thus, metabolic acidosis in this model acts as a powerful trigger for both metabolic and pro-inflammatory cellular signaling pathways [34].

Treatment with Nuclex resulted in a dose-dependent normalization of acid-base balance. It was accompanied by an increase in pH, correction of bicarbonate level, and a decrease in base deficiency. The simultaneous decrease in *c-Myc* gene expression and suppression of the *Rela* gene in the experiment is consistent with the hypothesis that protonated Nuclex oligonucleotides are able to redistribute and buffer protons. At the same time, treatment with Nuclex reduces the acid load on cells and restores the stability of their signaling pathways. The most pronounced effect was ob-

served in the group receiving Nuclex at a dose of 0.15 mg/g. In this group, *Tnf* gene expression demonstrated the lowest variability, in contrast to the control and Met groups where high variability was evident.

The combined therapy of "Nuclex" + "Metabol-norm" also proved to be effective, demonstrating both maximum normalization of acid-base balance. At the same time, this therapy revealed optimal normalization of pro-inflammatory parameters and simultaneous increase in the level of *Ifny* expression gene. Such combined therapy may indicate synergy between the proton-modulating properties of "Nuclex" and the metabolic effects of "Metabol-norm". The results of this study confirm the assumption that the use of protonated nucleotides in metabolic acidosis may be a promising method of treating metabolic acidosis. The revealed effect of the studied drugs on pH-dependent signaling pathways opens up opportunities for the development of new metabolic-immunomodulatory agents for the treatment of acidosis.

The study of cytokine gene expression revealed a selective effect of Nuclex on their activity. The levels of *Il6* gene expression in the blood of mice during acidosis in control and under the influence of drugs demonstrate a wide range of values. Statistical analysis did not reveal any significant difference between the groups. It is known that IL-6 is a very variable cytokine, which was demonstrated in our experiment and Nuclex treatment does not demonstrate a pronounced effect on the *Il6* gene expression profile.

Tnf gene expression levels are represented by very high individual peaks in the Met and Nuc15 groups. The combination therapy group demonstrated the lowest variability of *Tnf*, in the absence of hyperinflammatory peaks. It has been shown that the drugs «Metabol-norm» and Nuclex can cause acute spikes in Tnf gene expression against the background of blood acidosis in mice. At the same time, their combination stabilizes *Tnf* gene expression and suppresses these peaks. Such activity of combination therapy indicates the ability of these drugs to most effectively normalize the NF-κB-dependent response.

It is important to emphasize the expression pattern of the type II interferon gene, *Ifny*, during metabolic acidosis in mice. The activity of the type I interferon genes, *Ifnα2* and *Ifnβ1*, remained relatively stable in our model and did not show significant intergroup differences. Conversely, the activity of the *Ifny* gene increased significantly under the influence of Nuclex, reaching its maximum values during combined therapy with Nuclex and Metabol-norm. The increase in *Ifny* gene expression without a parallel increase in the activity of the *Tnf* or *Il6* genes indicates a modification of the cellular immune response from a chaotic NF-κB-dependent activation to a more controlled Th1-oriented response [35]. This is consistent with the role of KLF transcription factors as regulators of T-cell program stability and metabolic homeostasis [36, 37]. The modest decrease in *Klf* expression under the influence of Nuclex may reflect the transition of cells from a stressed state to a more stable state. KLF transcription factor and its associated

factors regulate T-cell migration, quiescence, and metabolic programming. And their sensitivity to protonated forms of Nuclex oligonucleotides may indicate a pH-modulated regulation of transcription factors.

Taken together, the results obtained support our hypothesis that protonated Nuclex oligonucleotides function as metabolic and immune modulators. They are able to correct acid-base imbalance and reduce metabolic stress and glycolytic activation. This is manifested by a decrease in the activity of the *c-Myc* gene. This effect of Nuclex is mediated by the attenuation of NF-κB-dependent inflammation, in which the activity of the *Rela* gene is reduced and the activity of *Tnf* is stabilized. Ultimately, due to an increase in the activity of the *Ifny* gene, the immune response is directed towards an orderly activation of Th1.

Study limitations: One limitation of the study is that the acid-base disturbances occurred under real-world conditions of war, rather than within a standardized chemical model of metabolic acidosis. However, such conditions may reflect a biologically relevant variant of stress-induced metabolic disturbances associated with chronic neuroendocrine stress, exposure to high levels of noise and explosives typical of modern warfare.

Conclusion

The analysis of experimental results (box-and-whisker plots with statistical analysis and a correlation matrix) consistently demonstrates that Nuclex increases HCO_3^- levels and improves the BE value, stabilizing pH without necessarily lowering pCO_2 . This result indicates the Nuclex's ability to correct acid-base balance at the metabolic level. The beneficial effect of the drug Nuclex is attributed to the attenuation of NF-κB-dependent inflammation-accompanied by the reduced *Rela* gene activity and stabilized TNF activity-while the reduction in *Ifny* gene activity directs the immune response toward the orderly activation of Th1 cells. The results obtained under the uncontrolled conditions of martial law require validation using an

ethically approved experimental model that includes a healthy control group, anaerobic blood sampling, and measurements of lactate, electrolytes, renal function, and respiratory physiology.

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ВПЛИВ ПРЕПАРАТІВ «НУКЛЕКС» ТА «МЕТАБОЛ-НОРМ» НА КИСЛОТНО-ЛУЖНИЙ БАЛАНС ТА ЕКСПРЕСІЮ ВИБРАНИХ ГЕНІВ У КРОВІ МИШЕЙ

Метаболічний ацидоз є критичним компонентом інфекційних станів, зокрема вірусних захворювань із тяжким перебігом, і асоціюється з підвищеною захворюваністю та смертністю. Сучасні терапевтичні підходи до корекції ацидозу обмежені залежністю від респіраторної компенсації та ризиком перевантаження організму CO₂. Тому розробка нових засобів, здатних відновлювати буферну ємність без збільшення дихального навантаження, має важливе значення. **Метою** дослідження було оцінити вплив препаратів «Нуклекс» (комплекс протонованих олігорибонуклеотидів із D-манітолом) та «Метабол-норм» на показники кислотно-основного стану та експресію генів у крові мишей за умов метаболічного ацидозу. **Методу.** Дослідження проводили *in*

vivo на мишах лінії BALB/c. Аналізували показники газового складу крові (pH, pCO₂, HCO₃⁻, надлишок основ (BE)), а також рівні експресії транскрипційних факторів (*c-Мус*, *Klf*, *Sox2*, *Rela*, *Nfkb*) і генів цитокінів (*Ifnα2*, *Ifnβ1*, *Ifnγ*, *Il6*, *Tnf*) методом RT-qPCR. **Результати.** Застосування препарату «Нуклекс» призвело до значного підвищення pH, відновлення рівня бікарбонатів (HCO₃⁻) та зменшення дефіциту основ (BE), що свідчить про ефективну метаболічну корекцію ацидозу без зниження pCO₂. Натомість застосування лише «Метабол-норм» не забезпечило повної нормалізації цих показників. Найвираженіший ефект спостерігався при комбінованій терапії. На молекулярному рівні «Нуклекс» знижував експресію *c-Мус* і *Rela*, стабілізував рівень *Nfkb* та зменшував варіабельність *Sox2*, що вказує на нормалізацію метаболічного та запального стану клітин. Крім того, «Нуклекс» вибірково підвищував експресію *Ifnγ*, не впливаючи на *Ifnα2* чи *Ifnβ1*, що свідчить про зміщення імунної відповіді в бік контрольованого типу Th1. **Висновки.** Отримані результати підтверджують концепцію, згідно з якою протоновані олігорибонуклеотиди діють як небікарбонатні буферні агенти, здатні зв'язувати іони водню (H⁺), відновлювати резерви бікарбонатів і стабілізувати кислотно-основний гомеостаз. Отже, «Нуклекс» є перспективним засобом метаболічної та імунomodulatory терапії ацидозу при тяжких стресових та інфекційних станах.

Ключові слова: Нуклекс, Метабол-норм, показники газового складу крові, транскрипційні фактори, гени цитокінів.