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Cerium dioxide nanoparticles modulate the oxidative metabolism of neutrophils upon blood irradiation with a pulsed broadband UV source

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ABSTRACT The effect of CeO_2 nanoparticles on the oxidative activity of neutrophils under UV irradiation with a pulsed broadband UV source (210 mJ/cm^2) was analyzed. The effects of citrate-stabilized CeO_2 sol on spontaneous and stimulated by phorbol-12-myristate-13-acetate (PMA) and *N*-formylmethionyl-leucyl-phenylalanine (fMLP) luminol-dependent chemiluminescence of neutrophils were evaluated. The activating effect of CeO_2 nanoparticles on the spontaneous and suppressive effect on the stimulated chemiluminescence of blood neutrophils from apparently healthy donors was shown, with the most pronounced activating effect of CeO_2 nanoparticles revealed in the blood sample with initially high radical-producing cell activity. Under UV irradiation of blood at a dose of 210 mJ/cm^2 CeO_2 nanoparticles enhance both spontaneous and stimulated radical-producing function of neutrophils. Probably, the suppressive and activating effects of citrate-stabilised cerium dioxide sol may be due to the antioxidant activity of CeO_2 nanoparticles with respect to hypochlorite ions and prooxidant activity with respect to hydrogen peroxide.

KEYWORDS nanozymes, cerium dioxide nanoparticles, neutrophils, UV radiation, pulsed xenon UV lamp, chemiluminescence

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1. Introduction

One of the promising inorganic nanobiomaterials possessing enzyme-like activity along with unique physical and chemical properties is nanoscale cerium dioxide [1–7]. Biochemical activity of CeO_2 nanoparticles, being similar to the functions of a number of natural enzymes, such as superoxide dismutase (SOD) [8–11], catalase [12–14], peroxidase [15–18], phosphatase [19], phospholipase [20], photolyase [21], uricase [22], etc., expands the prospects for their biomedical application for the prevention, diagnosis, and therapy of socially significant diseases [23–25] and requires a comprehensive analysis of the properties of nanoscale cerium dioxide, including its interaction with blood components, both alone, and as part of combination therapy, for example, with ultraviolet irradiation of blood (UVIB).

The increased interest in the therapeutic potential of ultraviolet irradiation of blood is due to the emergence of new viral infections, including SARS, MERS, SARS-CoV-2 and their resistance to existing antiviral drugs, vaccines, and antibacterial drugs [26–29]. The therapeutic efficacy of UVIB has been demonstrated in a number of diseases, including diseases of the biliary tract, viral hepatitis, etc. [27, 30]. One of the main targets of UVIB exposure are immune cells – lymphocytes (T- and B-cells), neutrophils, macrophages, monocytes, dendritic cells [26, 30]. This brings attention to ultraviolet irradiation of blood for the treatment of autoimmune diseases and as a new immunomodulatory method [27,30]. The great potential of UVIB could be additionally expanded by the use of various substances, including those based on redox-active nanomaterials that can regulate the effectiveness of UVIB treatment, uncontrolled activation of neutrophils, and other indicators.

When CeO_2 nanoparticles enter the bloodstream, neutrophil granulocytes (neutrophils) are among the first cells to interact with them [31, 32]. Neutrophils are one of the most important and most active cells of the innate immune system, providing the first line of defense and responding to various antigens and damaging factors [33, 34]. Activated cells are able to secrete into the extracellular medium various low and high molecular weight substances with immunomodulatory or toxic effects [35–37]. Neutrophils are one of the main sources of free radicals in the body [38], and the mechanisms of their interaction with redox-active nanomaterials, primarily CeO_2 nanoparticles, require further research.

Here, a high-intensity pulsed xenon lamp was used as a source of UV radiation. Today it is one of the promising light sources for UV therapy as an alternative to traditional low-pressure mercury lamps. The main advantages of pulsed xenon lamps are a wide spectral range and high peak power with a relatively short exposure time. Since the state of the surface of nanomaterials is a key factor in the interaction with neutrophils [39, 40], citrate ions were used to functionalize cerium dioxide nanoparticles. Cerium dioxide nanoparticles stabilized by citrate ions possess high biocompatibility and low toxicity, and prevent hemocoagulation [41]. Though the bioactivity of CeO_2 nanoparticles modified with citrate ions has been widely studied, there are no data on their effect on blood neutrophils under ultraviolet irradiation.

In this study, we analyzed for the first time the effect of CeO_2 nanoparticles functionalized with citrate ions on the radical-producing activity of neutrophils upon UV irradiation of blood with a high-intensity pulsed xenon lamp.

2. Materials and methods

Cerium dioxide nanoparticles functionalized with ammonium citrate in a molar ratio of 1:1 were obtained in two stages. The initial electrostatically stabilized CeO_2 sol was synthesized by the thermal hydrolysis of an aqueous solution of cerium(IV) ammonium hexanitrate ($(NH_4)_2Ce(NO_3)_6$, #215473, Sigma) [42]. A solution of $(NH_4)_2Ce(NO_3)_6$ (100 g/L) was heated at 95 °C for 24 h. The resulting yellow precipitate was washed three times with isopropanol and then redispersed in deionized water. To remove residual isopropanol, a colloidal solution of cerium dioxide was boiled for 1 h under constant stirring. The concentration of the resulting CeO_2 sol, according to thermogravimetric analysis, was 20.6 g/L (0.12 M).

At the second stage, the surface of CeO_2 nanoparticles was functionalized with ammonium citrate (#247561, Sigma). An electrostatically stabilized CeO_2 sol was added to an aqueous solution of ammonium citrate (0.12 mol/L) under stirring. After addition of CeO_2 nanoparticles to the ligand solution, stirring was continued for 30 min.

Powder X-ray diffraction analysis (XRD) of powders obtained by drying colloidal solutions of cerium dioxide at 50 °C was carried out on a Bruker D8 Advance diffractometer (CuKα radiation, θ–2θ geometry).

Analysis of the microstructure of samples of CeO_2 sols was carried out by transmission electron microscopy (TEM) on a Leo 912 AB Omega electron microscope at the accelerating voltage of 100 kV.

UV-visible absorbance spectra were obtained on a SF-2000 spectrophotometer (OKB Spektr, Russia). The wavelength range was 200 – 700 nm, the scanning step was 0.1 nm.

The average hydrodynamic particle diameter of colloidal solutions of CeO_2 and the ζ-potential were determined at 20 °C using a Photocor Complex analyzer (25 mW, diode laser, $\lambda = 650$ nm).

As a source of neutrophilic granulocytes, we used venous blood of apparently healthy donors ($n = 3$, donors 1–3) aged 22 $\pm$ 1 years, sampled in tubes with an anticoagulant – lithium heparin (17 IU/mL). Biomaterial sampling was carried out by the qualified personnel. Donors signed an informed consent to participate in the study. The design of the study was approved by the Ethics Committee of the Research Centre for Medical Genetics (Protocol #5, May 2019). The samples were stored at $+4$ °C for no more than 1.5 – 2 hours from the moment of blood sampling.

The blood samples (600 μl) were preincubated with 30 μl of 1 mM citrate-stabilized CeO_2 sol for 30 min. A device for UV irradiation of blood (UVIB) based on an L11937 pulsed lamp (Hamamatsu, Japan) (device power 30 W, nominal lamp power 20 W) was used as a source of high-intensity pulsed broadband radiation. The distance from the radiation source to the sample was 10 cm. To assess the effect of CeO_2 nanoparticles on the functional activity of blood neutrophils during irradiation, a UV irradiation dose was chosen that did not cause significant activation of neutrophils, equal to 210 mJ/cm^2.

Analysis of the radical-producing function of blood neutrophils was performed by luminol-enhanced chemiluminescence [43]. We used the protocol of two-stage stimulation of the functional activity of cells: a primer + a main stimulus. Phorbol-12-myristate-13-acetate (PMA, #P148, Sigma) was used as a primer, and *N*-formylmethionyl-leucyl-phenylalanine (fMLF, #F3506, Sigma) was used as a main stimulus. The measurements were carried out in a medium consisting of Hank's buffer (PanEco, with glucose without phenol red) with Hepes (50 μM, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, #H3375, Sigma).

Cell luminescence was recorded at room temperature on a 12-channel Lum-1200 chemiluminometer (DISoft, Russia). An aliquot of 450 μl of medium (Hanks/Hepes) with 25 μl of blood was previously incubated with CeO_2 citrate sol. Next, 25 μl of 1 mM luminol solution (#123072, Sigma) was added to a cuvette. Spontaneous chemiluminescence of blood cells was recorded for 10 min. Next, neutrophils were primed by adding PMA (50 ng/mL) without interrupting the recording of the analytical signal (20 min after the addition of PMA). At the final stage, the main stimulus fMLF (10 μM) was added to the blood cells, registering the chemiluminescent response of the cells for at least 60 min.

PowerGraph software (version 3.3) was used to process chemiluminograms. Both for the spontaneous chemiluminescence and for PMA+fMLF-stimulated chemiluminescence we calculated the area under the curve (AUC) (S_{lum}, $S_{\text{PMA+fMLF}}$), which is proportional to the number of produced free radicals. To assess the effects of CeO_2 nanoparticles and UV irradiation, the activation (> 1) and suppression (< 1) coefficients were calculated as the ratio of the corresponding AUC S_{lum} or $S_{\text{PMA+fMLF}}$ to the control value (S_0). The response of neutrophils without exposure to CeO_2 nanoparticles and UV irradiation was considered as a control.

3. Results and discussion

3.1. Physicochemical characteristics of CeO_2 nanoparticles

The X-ray patterns of the dried initial CeO_2 sol (pH $\sim$ 3) obtained by the thermal hydrolysis of cerium(IV) ammonium hexanitrate and the citrate-stabilized colloidal solution of cerium dioxide are shown in Fig. 1a.

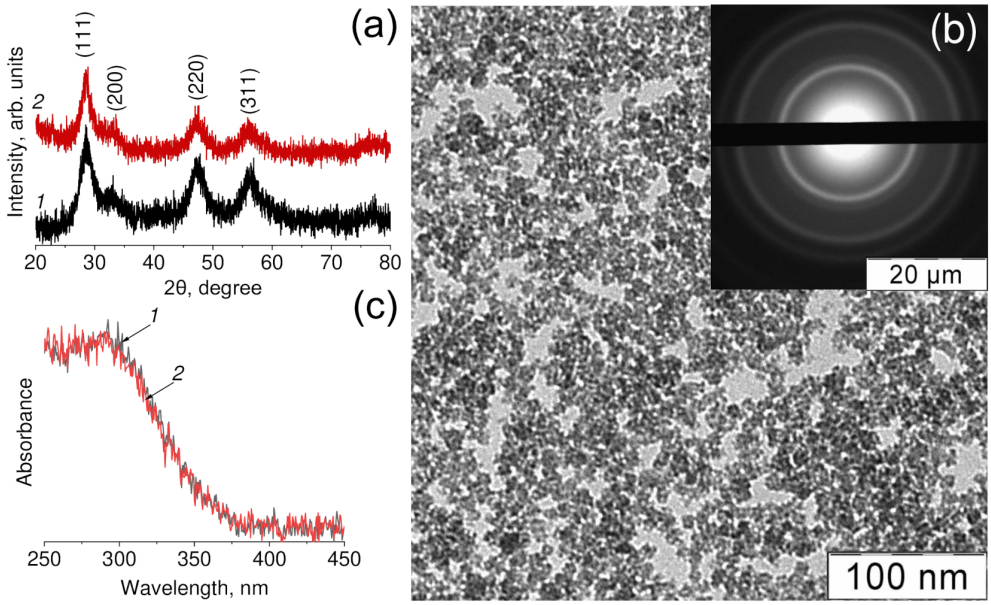

FIG. 1. XRD patterns of CeO_2 nanopowders (a); TEM images and electron diffraction data (inset) of CeO_2 nanoparticles (b); UV-visible absorption spectra of CeO_2 sols (c). Samples of nanoscale cerium dioxide: bare CeO_2 sol (1) and citrate-stabilized CeO_2 sol (2).

According to XRD data (Fig. 1a), CeO_2 sols contain single-phase cerium dioxide (PDF2 34-0394). The size of CeO_2 nanoparticles, estimated from the Scherrer equation, was 3.2 nm. The data on the particle size and the phase composition of the obtained material were confirmed by the results of analysis of the colloidal solution of CeO_2 by transmission electron microscopy (TEM) and electron diffraction (Fig. 1b).

Absorption spectra in the UV-visible region of the CeO_2 sols are shown in Fig. 1c. The appearance of an absorption band in the region of 280 – 300 nm confirms that the sols do contain nanoscale cerium dioxide.

The average hydrodynamic diameters of particles equal to 11 nm and 14 nm, respectively, were determined by dynamic light scattering for the samples of initial and citrate-stabilized CeO_2 sols. Small changes in the hydrodynamic diameter upon the interaction of cerium dioxide nanoparticles with the ligand indicate approximately the same degree of particle aggregation in colloidal solutions of CeO_2. Analysis of the electrokinetic properties of CeO_2 sols showed that functionalization of the surface of nanoscale cerium dioxide with citrate ions leads to a decrease in the absolute value of ζ-potential from $+41.2 \pm 1.5$ mV to $+15.3 \pm 0.9$ mV.

3.2. Analysis of the effect of CeO_2 nanoparticles on the radical-producing activity of neutrophils

Radical-producing activity of neutrophilic leukocytes was analyzed by luminol-enhanced chemiluminescence method using a two-step stimulation protocol [43, 44].

In the first series of experiments, we measured spontaneous chemiluminescence of neutrophils (Fig. 2a,c). In the second series, we measured chemiluminescence stimulated by the sequential addition of PMA and fMLF (Fig. 2b,d).

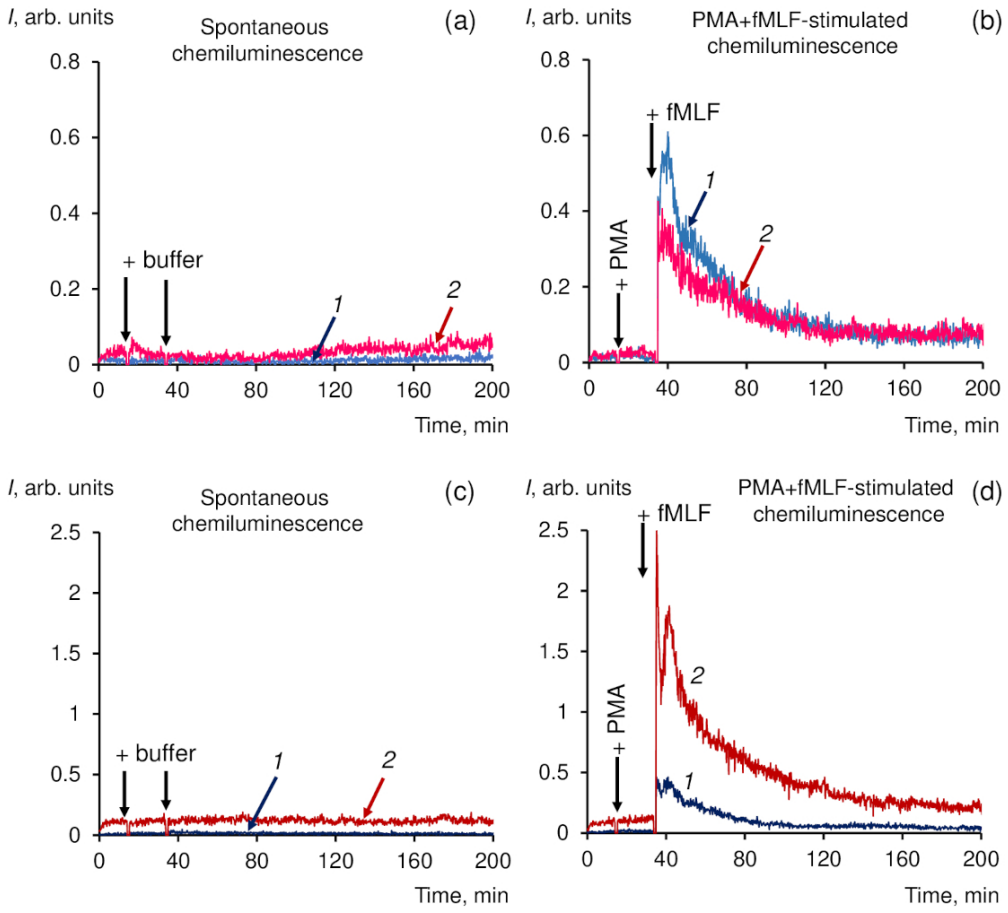

FIG. 2. The chemiluminograms of neutrophil response before (a, b) and after (c, d) exposure to UV irradiation (210 mJ/cm^2). Samples: control (without CeO_2) (1), with citrate-stabilized CeO_2 sol (2).

As for spontaneous chemiluminescence, the signal intensity was low ($I < 0.5$ arb. units, Fig. 2a,c). The sequential addition of the stimuli (PMA and fMLF) with various stimulation mechanisms leads to the extended chemiluminescent response of neutrophils (Fig. 2b,d). Stimulated chemiluminescence is a result of neutrophil priming (pre-activation) with PMA and subsequent activation with fMLF (Fig. 2b,d). As a result, neutrophils produce various types of reactive oxygen species (ROS), mainly, hydrogen peroxide and hypochlorite [45]. An increase in the intensity of chemiluminescence qualitatively indicates an increase in the radical-producing function of neutrophils after the addition of stimuli (Fig. 2b,d).

The used concentration of the colloidal CeO_2 solution of 50 μm does not affect cell viability [46–48]. To quantitatively assess the effect of CeO_2 nanoparticles on the neutrophils response before and after UV exposure, we calculated the AUC values (S_{lum}, $S_{\text{PMA+fMLF}}$), which are proportional to the amount of formed free radicals (Fig. 3).

To assess the effect of CeO_2 nanoparticles, including in combination with UV radiation, based on the ROS-producing activity of neutrophils (S_{lum}, $S_{\text{PMA+fMLF}}$, Fig. 3), the activation and suppression coefficients were calculated. A coefficient value > 1 indicates activation of the radical-producing function of neutrophils, and a coefficient value < 1 indicates suppression of the function (Table 1).

In the absence of UV radiation, the citrate-stabilized CeO_2 sol had an activating effect on the spontaneous chemiluminescence of neutrophils (Fig. 3a, Table 1). The most prominent effect of enhancing the ROS-producing activity of cells in the presence of CeO_2 nanoparticles was demonstrated by the sample from donor 3. It should be noted that in a series of control measurements (without CeO_2 nanoparticles), the sample from donor 3 was characterized by approximately 3.5 times higher radical-producing activity compared to the samples from donor 1 and donor 2. In turn, this could be the reason for the enhancement of stimulated chemiluminescence by CeO_2 nanoparticles from donor 3 (Fig. 3b, Table 1). At the same time, in the samples from donor 1 and donor 2, the suppressor effect of the citrate-stabilised CeO_2 sol was registered (Fig. 3b, Table 1). The most probable explanation for the observed effect is the competition between immunomodulatory and antioxidant effects caused by CeO_2 nanoparticles. On the one hand, nanoscale CeO_2 should induce an immune response; on the other hand, having antioxidant properties [49–51], CeO_2 nanoparticles are able to prevent the activation of the radical-producing function of neutrophils. Preincubation of neutrophils with citrate-stabilized CeO_2 sol demonstrates that cerium dioxide nanoparticles themselves can act as stimuli (Fig. 3a, Table 1). Obviously, the stimulating ability of nanoscale CeO_2 depends on the state of neutrophils and the immune system (presence of cytokines, etc.).

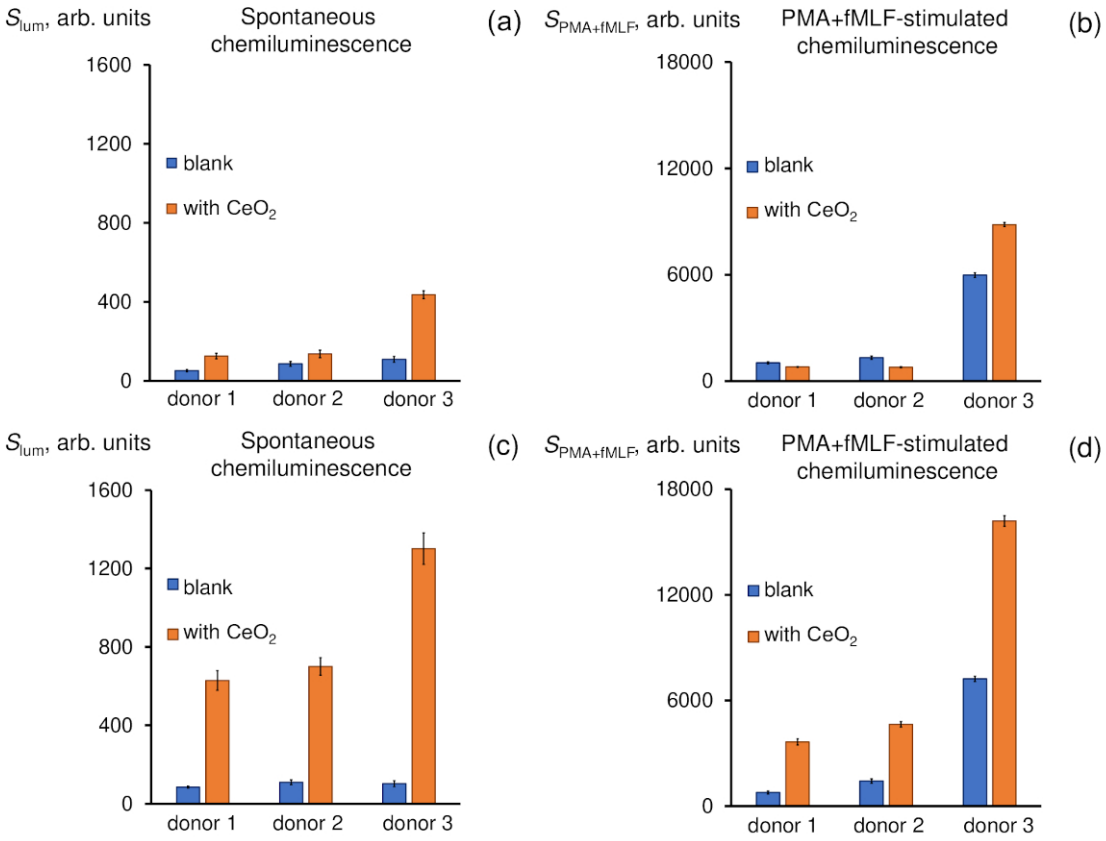

FIG. 3. Distribution histograms of indicators of radical-producing activity of neutrophils S_{lum} and $S_{PMA+fMLF}$, calculated from the data of spontaneous and stimulated chemiluminescence, respectively; before (a, b) and after (c, d) UV exposure (210 mJ/cm^2).

TABLE 1. Effect of citrate-stabilized CeO_2 nanoparticles (CeO_2 NPs) on spontaneous and stimulated chemiluminescence (CL) of neutrophils before and after UV exposure (average values of the activation and suppression coefficients are given)

CL	Spontaneous CL	PMA+fMLF-stimulated CL	Spontaneous CL	PMA+fMLF-stimulated CL
Factor determining the effect	CeO_2 NPs		CeO_2 NPs + UV exposure	
donor 1	2.4	0.8	12.2	4.5
donor 2	1.6	0.6	8.1	6.0
donor 3	4.0	*1.5	12.0	1.8

* – activation

The few available studies demonstrate the opposite effect – a decrease in ROS production by immune cells in the presence of CeO_2 nanoparticles [52,53]. Eriksson *et al.* showed that CeO_2 nanoparticles did not induce the production of free radicals in isolated neutrophils activated by PMA [52]. In these samples, nanoscale CeO_2 exhibited significant radical-scavenging properties [52]. Registration of the luminol-enhanced response of neutrophils makes it possible to trace the formation of the main types of free radicals. Luminol is a sensitive probe for hydrogen peroxide and hypochlorite ions [54–56] produced by NADPH oxidase (NOX2) and neutrophil myeloperoxidase. Moreover, in the absence of peroxidases, the luminescence of luminol can be caused by interaction with the superoxide anion radical [57]. In this study, it is likely that the suppressor effect in stimulated chemiluminescence in the samples from donor 1 and donor 2 could be due to the antioxidant activity of CeO_2 nanoparticles with respect to hypochlorite ions. The antioxidant activity of CeO_2 nanoparticles in relation to HOCl/ClO^- was demonstrated elsewhere [53]. The ability of nanoscale cerium dioxide to catalyze the decomposition of ClO^- ions by a reaction involving the reduction of Ce^{4+} to Ce^{3+} and the formation of

oxygen was confirmed in a series of *in vitro* and *in vivo* experiments [53, 58]. A significant decrease in myeloperoxidase activity in hepatocytes under the action of CeO_2 nanoparticles was also demonstrated [59]. Thus, the regulation of the oxidative activity of neutrophils by CeO_2 nanoparticles can occur both by direct inactivation of ROS and by suppressing the activity of cellular enzymes that produce free radicals.

In this study, it was found that the combined action of CeO_2 nanoparticles and pulsed broadband UV radiation at a dose of 210 mJ/cm^2 causes activation of neutrophils (Fig. 3c,d, Table 1). Irradiation of blood in the presence of citrate-stabilised CeO_2 sol significantly enhances both spontaneous and stimulated chemiluminescence (Fig. 3c,d). This effect can probably be due to the prooxidant activity of CeO_2 nanoparticles with respect to hydrogen peroxide. There are only few works devoted to the modulation of the oxidative metabolism of neutrophils by CeO_2 nanoparticles under UV radiation. Exposure of neutrophils to a low dose of UV radiation (500 mJ/cm^2) can enhance ROS formation due to NADPH oxidase activation [31]. In the same report, the ability of CeO_2 nanoparticles to significantly reduce the activity of NADPH oxidase and inhibit free radical processes was demonstrated. The inactivating effect of CeO_2 nanoparticles with respect to free radicals is explained by their catalase- and SOD-like properties [31]. The protective effect of CeO_2 nanoparticles against the damaging effect of UV radiation, due to the enzyme-like activity inherent in nanoscale cerium dioxide, was also observed in experiments with L929 fibroblasts [60]. According to the data, the protective effect also included an increase in the activity of cellular antioxidant enzymes in the presence of CeO_2 nanoparticles when compared with the control.

Thus, CeO_2 nanoparticles can have a variety of effects on living cells. The results obtained demonstrate the ability of CeO_2 nanoparticles to modulate the oxidative metabolism of the main cells of the immune system, neutrophils, and also to enhance the effects of UV radiation.

4. Conclusions

For the first time, the effect of CeO_2 nanoparticles (with or without UV irradiation) on free-radical producing activity of neutrophils was demonstrated. The modulating effect of citrate-stabilized CeO_2 nanoparticles reveals itself either as enhancement or inhibition of the production of free radicals by neutrophils. In the absence of additional stimuli, CeO_2 nanoparticles activate neutrophils. However, this activating effect is less than that of artificial stimuli. As for stimulated chemiluminescence of neutrophils, nanoscale cerium dioxide has the suppressive effect. Under UV irradiation of blood at a dose of 210 mJ/cm^2, CeO_2 nanoparticles enhance the radical-producing function of neutrophils. Hypothetically, the suppressing and activating effects of citrate-stabilised cerium dioxide sol may be due to the antioxidant activity of CeO_2 nanoparticles with respect to hypochlorite ions and their prooxidant activity with respect to hydrogen peroxide, respectively.

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