Atmospheric Reactive Oxygen Species and Some Aspects of the Antiviral Protection at the Respiratory Epithelium

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Abstract—The review summarizes literature data on molecular and biochemical mechanisms of nonspecific protection of respiratory epithelium. The special attention is paid to comprehensive analysis of up-to-date data on the activity of the lactoperoxidase system expressed on the surface of the respiratory epithelium which provides the generation of hypothiocyanate and hypoiodite in the presence of locally produced or inhaled hydrogen peroxide. Molecular mechanisms of production of active compounds with antiviral and antibacterial effects, expression profiles of enzymes, transporters and ion channels involved in the generation of hypothiocyanate and hypoiodite in the mucous membrane of the respiratory system in physiological and pathological conditions (inflammation) are discussed. A hypothesis about the effect of atmospheric air composition on the efficiency of hypothiocyanate and hypoiodite generation in the respiratory epithelium in the context of its antibacterial and antiviral protection is presented. The causes and consequences of insufficiency of the lactoperoxidase system caused by the action of atmospheric factors are discussed in the context of controlling the sensitivity of the epithelium to the action of bacterial agents and viruses. Good evidence exists that restoration of the lactoperoxidase system activity can be achieved by application of pharmacological agents aimed to compensate for the deficit of halides in tissues, and by the control of chemical composition of the inhaled air.

Keywords: lactoperoxidase, hypothiocyanite, hypoiodite, reactive oxygen species, reactive nitrogen species, respiratory epithelium

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INTRODUCTION: MODERN CONCEPTS ON HYPOTHIOCYANATE AND HYPOIODITE PRODUCTION BY MUCOUS EPITHELIAL CELLS

Local production of reactive oxygen species (ROS) protects the respiratory mucosa from pathogenic agents, including bacteria and viruses [1]. Despite the fact that the generation of ROS is more often associated with mechanisms of mucosal cell damage due to the development of oxidative stress and accompanying inflammation [2], experimental and clinical data suggest that this ROS generation is relevant from the viewpoint of protective mechanisms implementation, and this is not directly related to the ROS formation by activated phagocytes. For example, it has been shown that suppression of ROS production by lung epithelial cells leads to a loss of antibacterial protection on the mucosal surface in experimental animals in vivo [1]; in the animal and human epithelial cells in vitro the antiviral activity and survival of these cells correspond to the intensity of ROS production by activated phagocytes. For example, it has been shown that suppression of ROS production by lung epithelial cells leads to a loss of antibacterial protection on the mucosal surface in experimental animals in vivo [1]; in the animal and human epithelial cells in vitro the antiviral activity and survival of these cells correspond to the intensity of ROS production in them [3]. The action of bacterial and viral agents on epithelial cells (directly or indirectly due to the effects of cytokines secreted by activated immunocompetent cells) leads to activation of intracellular signal transduction, resulting in Nrf2-dependent changes in gene expression and metabolism, ROS overproduction, induction of anti-
oxidant systems and stress -response of the cell [4, 5] (Fig. 1).

It is known that intracellular ROS are synthesized due to the activity of a number of enzymes, particularly, proteins I and III of complexes of the mitochondrial respiratory chain, cytoplasmic NADPH oxidase (NOX/DUOX), xanthine oxidase, cytochrome P450, polyamine and amine oxidases; in addition, many cells produce reactive nitrogen species (RNS), for example, peroxynitrite, due to the activity of NO synthase [5–7]. Unlike ROS, hydrogen peroxide, as well as peroxynitrite, hypochlorite, and singlet oxygen do not contain unpaired electrons and, as a result, have a lower reactivity. H₂O₂ is a product of the catalytic conversion of the superoxide anion radical (O₂⁻) by superoxide dismutase, and generators of the superoxide radical anion for this reaction are either mitochondrial enzymes (further, O₂⁻ is transported from the mitochondria to the cytosol by voltage-gated VDAC anion channels in megachannels in the contact sites between the inner and outer mitochondrial membranes), or localized in the cytoplasmic membrane of cells NADPH oxidase (generated O₂⁻ can be converted in this case to H₂O₂ in the extracellular space or transported back to the cytosol due to activity of chloride channels) [8]. Some cells can capture H₂O₂ from the extracellular space due to the activity of aquaporins (known in this context as peroxyporins), particularly AQP8 [8, 9] (Fig. 2).
Bronchial epithelial cells are equipped with enzymes and ion channels/transporters responsible for the local production and realization of the effects of ROS, RNS, hydrogen peroxide and peroxynitrite. For example, H$_2$O$_2$ production by epithelial cells is typical both for physiological conditions and chronic inflammation in the mucous membrane of the bronchial tree; the latter implies the existence of mechanisms responsible for effective elimination of hydrogen peroxide [10]. In the epithelium of the bronchial tree, the hydrogen peroxide production is realized by NADPH oxidase (the isoform DUOX—dual oxidase); expression of this enzymes increased during differentiation of epithelial cells is controlled by Th2 cytokines (IL-4, IL-13) [11] (Fig. 1). This enzyme is a calcium-dependent flavoprotein that catalyzes superoxide anion radical formation and its conversion to hydrogen peroxide on the mucosal surface. Different DUOX isoforms are present not only in the epithelial cells of the bronchial tree, but also in the epithelium of other organs, for example, in the urothelium, as well as in the vascular endothelial cells, in the cells of the thyroid follicles [12, 13].

The DUOX expression changes in the dynamics of maturation of the epithelial cells of the respiratory tract, particularly, in the pulmonary epithelial cells of the human fetus, the maturation processes are accompanied by an increase in the expression of the DUOX1 isoform and, accordingly, the production of hydrogen peroxide and H$^+$ intracellular concentrations in vitro and in vivo, reaching in the latter case, the maximum at the time of birth; this may reflect the activity of the mechanisms that prepare the respiratory epithelium to meet pathogens in the early postnatal period [14]. At

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**Fig. 2.** Formation and conversion of intracellular and extracellular pools of hydrogen peroxide, providing production of hypothiocyanate and hypiodite on the surface of epithelial cells of the respiratory tract mucosa. SOD, superoxide dismutase; LPO, lactoperoxidase; NIS, sodium iodide symporter.
the same time, such expression pattern may have a species-specific character, since the expression of DUOX1 and lactoperoxidase (LPO) in lambs is significantly lower in the prenatal period of development and at the time of birth, but it significantly increases with the organism maturation [15].

Utilization of hydrogen peroxide depends on LPO activity, which is expressed by epithelial cells, and to a greater extent in the bronchi than in the trachea [10]. It is known that in the epithelium of the bronchial tree there are three main types of cells: (1) ciliated cells; (2) mucus-producing cells; (3) basal cells that function as epithelial progenitor cells. It is believed that only ciliated cells express DUOX, and under conditions associated with the loss of these cells (for example, in bronchial asthma and chronic bronchitis), the efficiency of H₂O₂ production decreases, while LPO is expressed predominantly by mucus-producing cells [10].

Hypothiocyanate (OSCN⁻) is a compound that is formed endogenously by LPO utilizing thiocyanate (SCN⁻) and H₂O₂ (Fig. 1). SCN⁻ is found in many biological tissues and fluids, particularly, in blood, saliva, milk, bronchoalveolar and nasal secretions, tears, gastric juice; its concentrations vary from tears, gastric juice; its concentrations vary from 0.01 mM to 3 mM [16]. The total concentration of SCN⁻ in the secretion on the surface of epithelial cells of the respiratory tree reaches 460 μM (in the exhaled air—27 nM), hydrogen oxide—5 mM (in the exhaled air—0.7 nM) [17, 18].

Besides thiocyanate, iodide (I⁻) can be a substrate for LPO, myeloperoxidase (MPO), and eosinophilic peroxidase; in the presence of hydrogen peroxide it is converted into hypoiiodite (IO⁻) through I₂ as the intermediate product. OI⁻ and I₂ have basically the same targets as hypothiocyanate: sulfhydryl groups of proteins, NAD(P)H. It also inhibits glycolysis enzymes, pentose phosphate pathway, and mechanisms of glucose transport into cells. In general, in the body, I⁻ acts as a free radical scavenger due to its reducing properties; it is also easily oxidized by peroxidases thus converting into hypoiodite (IO⁻), hypoiodic acid (HIO). Experimental studies have shown that hypoiodite has a pronounced antibacterial effect including antibacterial action against various types of microorganisms in biofilms [19]. The source of iodide for the production of hypoiodite in epithelial cells can be the thyroid hormone tetraiodothyronine (T₄) delivered to these cells; T₄ undergoes deiodination in peripheral tissues catalyzed by selenium-dependent deiodinases. For example, D2 deiodinase expressed in epithelial cells of the bronchial tree [20] can participate in the release of iodide for its subsequent conversion to hypoiodite (Fig. 2). It is known that in the epithelial cells of the thyroid gland, mammary and salivary glands, the iodide transport across the membrane occurs via the sodium iodide symporter (NIS), and its expression was detected in the respiratory epithelium [21].

Interestingly, in the bronchial epithelial cells, SCN⁻ transport across the membrane depends on the presence of sodium ion and competes with iodide; this suggests possible involvement of the sodium iodide symporter (NIS) in thiocyanate transport [22]. In other words, the presence of thiocyanate and iodide hinders SCN⁻ transport across the cell membrane. Other molecules can also transport iodide across the cell membrane: CFTR (a chloride channel known as cystic fibrosis transmembrane conductor regulator—a regulator of transmembrane permeability, aberrantly expressed in cystic fibrosis), calcium-dependent transporter anoctamine 1 (Ano1—Transmembrane member 16A—TMEM16A), pendrin, a chloride/iodide transport protein (Solute carrier family 26, member 4—SLC26A4) [23, 24] (Fig. 3).

As we have mentioned above, in addition to LPO, the thiocyanate conversion to hypothiocyanate can be performed by MPO and eosinophilic peroxidase; activation of these enzymes accompanies inflammation processes [25–27]. In this context, it is obvious that their activity will significantly increase in the respiratory tract mucous membrane during inflammation accompanied by leukocyte migration. In all cases, the mechanism is realized in two ways: (1) SCN⁻ oxidation with the formation of thiocyanogen SCN₂, which is rapidly hydrolyzed in the aqueous phase to hypothiocyanic acid HOSCN, which is present in solution in equilibrium with OSCN⁻; (2) direct OSCN⁻ production from SCN⁻. All the resulting products—OSCN⁻, HOSCN, SCN₂ then interact with sulfhydryl groups of proteins and form sulfenylthiocyanate derivatives (R-S-SCN). In addition, they can modify aromatic amino acids in proteins (tyrosine, tryptophan), amino groups, as well as NADP and NADPH (converting the latter into the oxidized form of pyridine nucleotides—NAD₂) [28] (Fig. 4).

It should be noted that overproduction of hydrogen peroxide leads to LPO inactivation, but in the presence of flavonoids, the activity of this enzyme is effectively restored [29]. Interestingly, LPO functions in close interaction with the CFTR chloride channel (in this context, it acts as a transporter of thiocyanate and iodide) and DUOX (NADPH oxidase generating hydrogen peroxide, the activity of which can be judged by the amount of H₂O₂ in exhaled air) in epithelial cells [30–32]. LPO activity increases with a decrease in pH, at least to 5.7–6.8 [33], and also depends on the bioavailability of SCN⁻.

Another important aspect of the realization of biological effects on the epithelial surface may be the LPO activity towards RNS: as soon as LPO is able to convert NO₃ to NO₂, being functionally coupled with xanthine oxidase, which generates O₂⁻ and hydrogen peroxide [34], it can be assumed that, in addition to
DUOX, xanthine oxidase can play the role of a H₂O₂ supplier for LPO. However, whether such mechanism (including in the context of the formation of peroxynitrite and the subsequent generation of nitrosothiols) operates in the epithelium of the respiratory tract remains unclear (Fig. 2). It is noteworthy that NO₃⁻ acts as one of the anions transported by the NIS-symporter [21], which raises new questions about the nature of the interaction of nitric oxide with the hypothiocyanate and hypoiodite-generating systems of cells.

Thus, increased ROS production, particularly, the superoxide anion radical, in the bronchial epithelial cells and subsequent conversion of O₂⁻ to hydrogen peroxide lead to LPO-dependent generation of hypothiocyanate and hypoiodite, which have various biological effects.
1. BIOLOGICAL EFFECTS OF (HYPO)THIOCYANATE AND (HYPO)IODITE ON THE SURFACE OF THE EPITHELIAL MUCOSA

Thiocyanate produced by epithelial cells acts as a free radical scavenger, and the thiocyanate concentration in biological fluids increases under the action of certain environmental factors, particularly, smoking and a vegetarian diet (for example, cabbage plants are a significant source of thiocyanate for mammals) [18]. In addition, thiocyanate exhibits protonophoric activity in the cell mitochondria, and this leads to mitochondrial swelling and uncoupling of oxidative phosphorylation [35]. This is probably why thiocyanate acts both as a cytoprotective antioxidant and as a cytotoxic agent [16, 36]. Interestingly, thiocyanate was tested as a therapeutic component in the therapy of arterial hypertension and cystic fibrosis [16].

Hypothiocyanate formed in tissues from thiocyanate is able to oxidize proteins by acting on their SH-groups with the formation of disulfide bonds, to decrease the intracellular level of reduced glutathione, but can be rapidly degraded in vivo [16]. In particular, the targets for the action of hypothiocyanate are the SH-groups of cysteine in the glycolytic enzymes (glyceraldehyde-3-phosphate dehydrogenase (GAPD), hexokinase, aldolase) as well as glucose-6-phosphate dehydrogenase (G6PD), and this is considered as an important component of the bactericidal effect of OSCN⁻ [36]. It is likely that decreased activity of key glycolytic enzymes can also act as a feedback mechanism for suppressing overactivation of tissue macrophages as macrophage polarization towards cytotoxic and pro-inflammatory phenotype requires activation of glycolysis [37] (Fig. 5). The antiviral effect of hypothiocyanate has been described and fairly well studied, for example, against the influenza virus [38], and more recently, a similar approach has been proposed for SARS-Cov-2 when testing the activity of a combination of OSCN⁻ with lactoferrin, or an aerosol containing OSCN⁻ [39]. It is particularly interesting that in vitro at pH 6.0, saliva HOSCN/OSCN⁻ decreased viability of respiratory syncytial virus (RSV) with IC₅₀ value of 8.0 μM [40]. RSV, as well as adenovirus, are also targets for HOI in the pH range from 7.0 to 8.0: iodide oxidation catalyzed by LPO completely blocked the reproduction of viruses in vitro, thus suggesting efficiency of iodine preparations for the prevention of viral infections the upper respiratory tract mucous membranes [41]. Later, this suggestion was confirmed in direct experiments [15]: intragastric administration of potassium iodide to newborn lambs led to a tenfold increase in the local concentration of iodide in the mucous membrane of the respiratory tract, and subsequent intratracheal administration of RSV caused inflammation that did not reach the degree of severity found in control group, and this protective effect of potassium iodide was abolished by the suppression of LPO activity by dapsone. Thus, despite the fact that OSCN⁻ was not effective against adenovi-
It is possible that such mechanism may account for the reduced resistance of the respiratory mucosa to pathogens of bacterial and viral respiratory infections in this disease.

However, it should be remembered that besides CFTR, cytokine-regulated transporters may be involved in the SCN\(^{-}\) transport across the cell membrane; for example, pendrin (encoded by SLC26A4; its expression in lung tissue is enhanced under the action of IL-4, IL-13, and IL-17) [46], calcium-dependent chloride channels, for example, anoctamin-1 (TMEM16A; its expression is under stimulatory control by IL-4 and IL-13) [16, 47–49]. Thus, it is reasonable to suggest that the ratio of pro-inflammatory (IL-13, IL-17) and anti-inflammatory (IL-4) cytokines, dynamically changing during inflammation, can significantly change the activity of hypothiocyanate- and hypoiodite-generating enzyme systems on the surface of the respiratory epithelium (Fig. 1).

It is important to note that the localization of iodide, thiocyanate, and chloride transporters in epithelial cells is different: NIS is expressed in the basement membrane, providing transport of thiocyanate and iodide from the blood into the cell, while pendrin, CFTR, Ano1 are expressed in the apical membrane, thus transporting thiocyanate and iodide into the extracellular space and in the case of bronchial epithelium into the secret on the surface of the mucous membrane of the respiratory tree [23]. In addition, the sodium-dependent multivitamin transporter SMVT (SLC5A6), exhibiting a high degree of homology with the NIS protein, is also involved in iodide transport, while [50] (Fig. 3).

Pendrin is involved in the transport of iodide from cells, at least in the thyroid gland, and its decreased expression is manifested by the development of goiter [51]. Interestingly, IL-4 and IL-13 stimulate expression of CFTR, DUOX in lung epithelial cells [52]. IL-13, in turn, can be produced by bronchial epithelial cells [53] and activated lymphocytes [54], thus causing a disorganizing and remodeling effect on ciliated epithelial cells as well as bronchial hyperreactivity, fibrogenic action, and local hypersecretion of mucus [55]. Thus, it is reasonable to suggest that an increase in the
production of IL-13 and its effect on bronchial epithelial cells will result in an intensification of the production of hypoiodocyanate and, possibly, hypoiodite; in the acute period of inflammation this will improve the antibacterial and antiviral protection of the mucosa, and not only due to enhanced generation of these compounds, but also due to an increase in mucus production [56]. On the other hand, the same events may contribute to the realization of the profibrogenic effect of IL-13, manifested as the development of subepithelial fibrosis, which will lead to long-term negative consequences due to airway remodeling.

How significant is the hypoiodite contribution to the total protective effect of the products of the LPO reaction? As mentioned above, in the case of RSV, it was demonstrated in vivo that hypoiodite exhibited a more pronounced inactivating effect as compared to hypoiodocyanate (when potassium iodide is administered intragastrically before intratracheal inoculation of RSV in animals) [15], and in the case of oral administration of potassium iodide to humans (leading to the accumulation of I– in the secretion of the upper bronchial tree) [41]. In vitro experiments also revealed hypoiodite efficiency of the influenza virus, and the effectiveness of LPO-generated hypoiodite depended on the strain of the influenza virus [31]. Recently, a potential antiviral effect of iodide has been suggested against SARS-Cov-2, which could be achieved by using potassium iodide, accumulating in the secretion of the bronchial mucosa [57].

2. ATMOSPHERIC FACTORS
IN THE LACTOPEROXIDASE MECHANISM OF MUCOSAL EPITHELIUM PROTECTION

The mechanisms of action of ROS and iodine in the inhaled air, as well as atmospheric pollutants in relation to the accumulation and production of hypoiodocyanate and hypoiodite by the LPO system in mucus on the surface of the epithelium of the bronchial tree still require deeper studies and better understanding.

Some atmospheric factors directly affect the content of LPO substrates or the concentration of its products, hypoiodocyanate and hypoiodite. For example, the hydroperoxyl radical, being a natural product of ozone decay in the troposphere and having a high photoperiodicity [58], easily enters the aqueous phase of the epithelial mucus. In aqueous solutions, the hydroperoxyl radical and superoxide anion O$_2^-$ are in equilibrium:

$$O_2^- + H_2O \leftrightarrow HO_2^- + OH^-.$$  

The equilibrium constant of this process is $pK_a = 4.88$.

The disproportionation reaction results in formation of hydroxide peroxide, one of LPO substrates. At neutral pH, about half of HO$_2^-$/$O_2^-$ is converted to hydrogen peroxide in 1 h:

$$\text{HO}_2^- + \text{HO}_2^- \rightarrow \text{H}_2\text{O}_2 + \text{O}_2,$$

$$\text{HO}_2^- + \text{O}_2^- + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 + \text{OH}^-.$$

The photoperiodicity of the atmospheric hydroperoxyl radical concentration is a possible mechanism for the photoperiodicity of the hydrogen peroxide concentration in water bodies [59] and atmospheric aerosols. The method for direct increase of hydrogen peroxide concentration in the inhaled air to improve the production of hypoiodocyanate in the respiratory tract was previously proven in a patent [60].

The non-enzymatic mechanism of formation of hypoiodocyanate and cyanogen in the presence of ROS in the aqueous phase occurs due to interaction with another product of ozone photodecomposition, the hydroxyl radical [61]:

$$\text{SCN}^- + 2\text{HO}^- \rightarrow \text{OSCNO}^- + \text{H}_2\text{O},$$

$$\text{OSCNO}^- + \text{SCN}^- + \text{H}_2\text{O} \rightarrow (\text{SCN})_2 + 2\text{OH}^-.$$  

The photochemistry of atmospheric iodine is also directly related to the photochemistry of ozone [62]. Photodissociation of organic iodine-containing compounds and molecular iodine over the surface of oceans and glaciers leads to the appearance of atomic iodine in the atmosphere:

$$\text{CH}_2\text{I}_2 + \text{hv} \rightarrow \text{CH}_2 + 2\text{I},$$

$$\text{CH}_2\text{IBr} + \text{hv} \rightarrow \text{CH}_2 + \text{I} + \text{Br},$$

$$\text{I}_2 + \text{hv} \rightarrow 2\text{I}.$$  

Subsequent interaction with ozone leads to the formation of iodine monoxide. Iodine monoxide interaction with the hydroperoxyl radical results in hypoiodous acid formation [63]:

$$\text{I} + \text{O}_3 \rightarrow \text{IO} + \text{O}_2,$$

$$\text{IO} + \text{HO}_2 \rightarrow \text{HOI} + \text{O}_2.$$  

In water hypoiodous acid dissociates with hypoiodite formation [64]:

$$\text{HIO} \rightarrow \text{H}^+ + \text{IO}^-.$$  

It should be noted that a weak solution of free iodine also forms hypoiodous acid [65]:

$$\text{I}_2(aq) + \text{H}_2\text{O} \rightarrow \text{HIO} + \text{H}.$$

Besides the above mentioned iodine compounds, iodite ion I$_2^-$, triiodite ion I$_3^-$, iodic acid HIO$_3$ and iodate anion IO$_3^-$ are formed in water. However, only molecular iodine and iodic acid have biocidal activity [66]. The mechanism of the antibacterial and antiviral action of a number of iodine-containing drugs (e.g., povidone-iodine) is associated with the formation of
The high efficiency of local application of povidone-iodine by irrigation of the oral cavity and nasopharynx in relation to a number of bacterial and viral pathogens of the respiratory tract is shown in [68]. However, it should be noted that molecular iodine and iodic acid in solution are in equilibrium, and their ratio depends on pH. At pH 7.0, the ratio $I_2/HIO = 52/48$, but small shifts in pH, have a significant impact on this ratio. For example, at pH 6.0 $I_2/HIO = 90/10$, and at pH 8.0 $I_2/HIO = 12/88$. These ratios establish the relationship between the ratio of concentrations and the pH of the medium:

$$\log \left( \frac{I_2}{HIO} \right) = -0.91(pH) + 6.41.$$  

Since the pH value of the secretion of healthy broncho-pulmonary epithelium is slightly acidic (pH 6.6) [69], it corresponds to a 2.5-fold excess of the concentration of molecular iodine over iodic acid, and under various pathological conditions the pH value of the mucus shifts to the alkaline values. For example, in cystic fibrosis pH 6.8, in smokers pH [6.8–7.3], in chronic bronchitis pH [7.6–7.8], rhinitis pH [7.2–8.3], in acute respiratory viral infection pH [7.2–8.3] and in bacterial infection pH [7.2–7.4] [69]. In this case, the balance is shifted towards an increase in the production of iodic acid and the values of the HIO/I$_2$ ratio can reach 0.6, 1.7, 4.9, 13.9, 13.9 and 2.1, respectively. Thus, the presence of dissolved iodine in the mucus in these pathological conditions will result in greater production of the more biocidal hypoiodous acid and non-enzymatic production of hypoiodite ions.

The presence of these natural factors in the inhaled air has a positive effect on the antibacterial and antiviral properties of the LPO system [15, 31, 33]. Studies of the mechanism of action of inorganic anions present in atmospheric air as pollutants on the activity of the LPO system [70] have shown that they cause significant competitive inhibition of hypothiocyanate formation. For example, the presence of NO$_3^-$ leads to a decrease in the binding constant of thiocyanate by 4.3 times, CN$^-$ by 5.8 times, and F$^-$ by 1.3 times. Iodide I$^-$ reduces this parameter by 10 times, and bromide Br$^-$ by 7.8 times. Iodide I$^-$, bromide Br$^-$, as well as chloride Cl$^-$ anions are inorganic anions present both in the secret of the pulmonary tract and in the composition of aerosols of sea air. At the same time, as a part of LPO and MPO systems in the presence of hydrogen peroxide, they exhibit significant antiviral activity [71]. However, it should be noted that the antiviral effect in the LPO/H$_2$O$_2$ system is more pronounced in NaI—log(TCID$_{50}$/mL) = 0.7 ± 0.1—at an initial level of 5.2 ± 0.07 than for NaBr—log (TCID$_{50}$/mL) = 1.1 ± 0.88—and even more than in NaCl—log(TCID$_{50}$/mL) = 5.0 ± 0.19. However, in the MPO/H$_2$O$_2$ system, the antiviral activity of NaCl—log(TCID$_{50}$/mL) = 1.2 ± 0.22—becomes significantly higher due to the hypochlorite anion production (these data were obtained in phosphate buffer at pH 6.0). An increase in the presence of MPO in bronchopulmonary secretion is possible only with the development of a pathological process. We can talk about the replacement of thiocyanate by more active halides for the implementation of antiviral protection during inflammation, and iodides are the most effective here [15].

The role of nitrous gases, particularly NO$_2$, as an antiviral and antibacterial protection factor in the LPO system is not entirely clear; however, the role of these pollutants in increasing morbidity and mortality from COVID-19 has been demonstrated [72–74]. In this regard, it can be assumed that nitrite anions do not lead to the formation of effective virucidal compounds and, on the contrary, contribute to a decrease in the resistance of the respiratory tract mucosa to the action of pathogens of infectious inflammation.

**CONCLUSIONS**

The mucosal epithelium of the respiratory tree is equipped with a variety of enzymatic systems and associated molecules (ion channels, transporters) required for efficient generation of endogenous compounds with antibacterial and antiviral activity. The formation of hypothiocyanate and hypoiodite due to the activity of LPO or leukocyte MPO in the presence of hydrogen peroxide provides protection for the epithelium under physiological conditions and during the development of infectious inflammation. The efficiency of hypothiocyanate and hypoiodite production depends on local factors (maintenance of enzyme systems and transporters, bioavailability of substrates) and systemic factors (effects of thyroid hormones, production of cytokines with pro- and anti-inflammatory activity, intake of halides with food, amount of ROS in the composition of inhaled air). The insufficiency of this system, caused by the action of atmospheric factors, may be the reason for the high sensitivity of the epithelium to the action of bacterial agents and viruses. Restoration of the activity of the LPO system can be achieved by using pharmacological agents that compensate for the lack of halides and, probably, by correcting the production and effects of cytokines.

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The authors declare that they have no conflict of interest. This work was not related to studies on humans or animals as research objects.
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