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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 hypothiocyanite 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 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-

Abbreviations used: Ano1—anoctamin 1 (transmembrane member 16A—TMEM16A); AQP8—aquaporin 8; CFTR—cystic fibrosis transmembrane conductor regulator; COVID-19—coronavirus disease 2019; DUOX—DUOX NADPH oxidase (dual oxidase); EPO— eosinophil peroxidase; IL— interleukin; LPO—lactoperoxidase; MPO—myeloperoxidase; NF-κB—transcription factor (nuclear factor kappa-light-chain-enhancer of activated B cells); NIS—sodium iodide symporter; NOX—NADPH oxidase; Nrf2—transcription factor (NF-E2-related factor 2); RSV—respiratory syncytial virus; SARS-Cov-2—severe acute respiratory syndrome-related coronavirus; RNS—reactive nitrogen species; ROS—reactive oxygen species; SLC26A4—solute carrier family 26, member 4; SMVT(SLC5A6)—sodium dependent multivitamin transporter; T_4—tetraiodothyronine; VDAC—voltage dependent anion channel.

† Deceased.

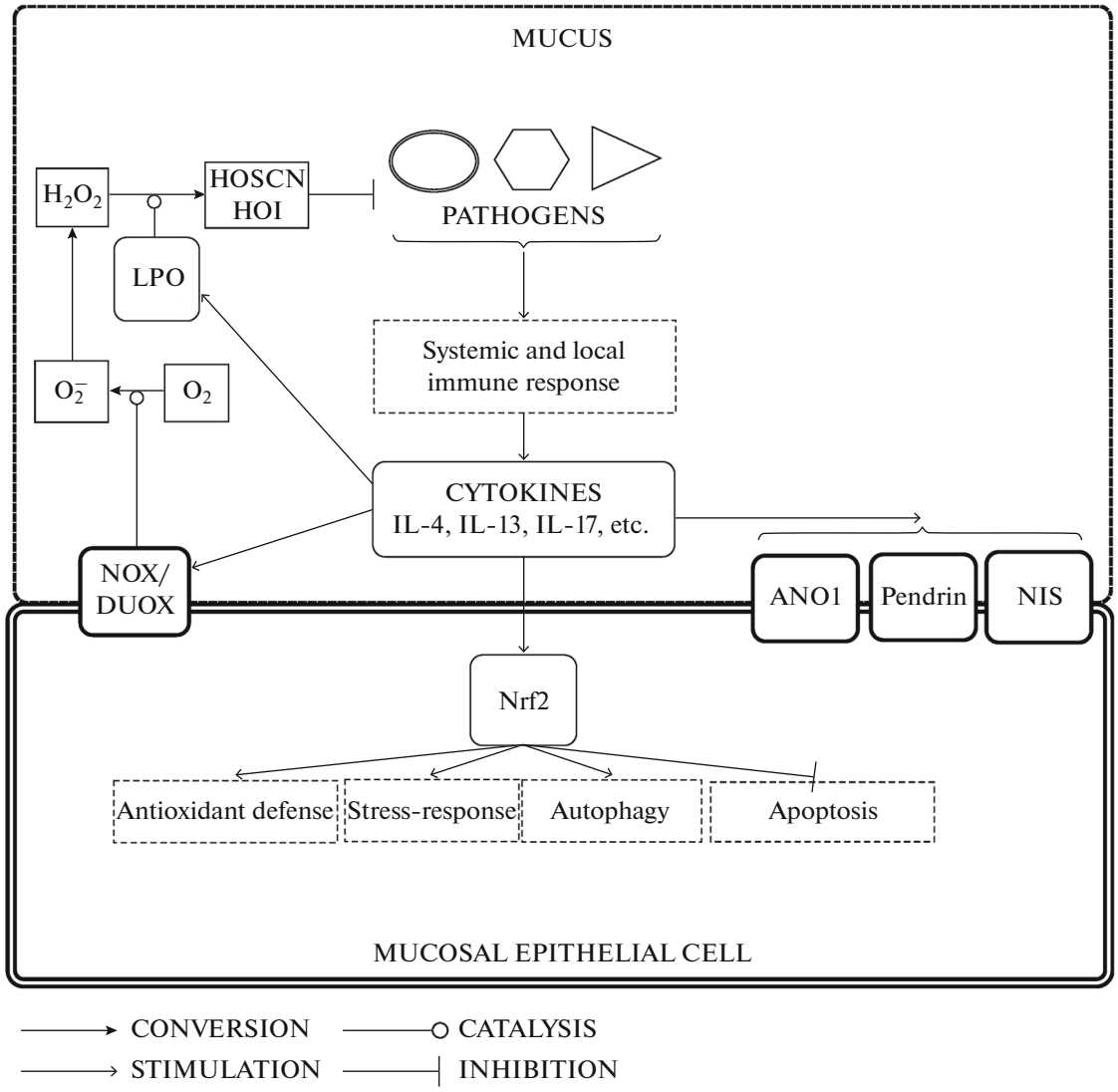

Fig. 1. Key mechanisms of activation of epithelial cells of the respiratory tract mucosa during bacterial and viral infections, associated with cytokine-mediated induction of the activity of NADPH oxidases (NOX/DUOX), lactoperoxidase (LPO) and substrate transporters of reactions catalyzed by them (anoctamin 1 Ano1, sodium iodide symporter NIS, pendrin), production of the superoxide radical anion O_2^-, hydrogen peroxide and its derivatives (hypothiocyanate HOSCN, hypoiodite HOI).

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. H_2O_2 is a product of the catalytic conversion of the superoxide anion radical (O_2^-) by superoxide dismutase, and generators of the superoxide radical anion for this reaction are either mitochondrial enzymes (further, O_2^- 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 O_2^- can be converted in this case to H_2O_2 in the extracellular space or transported back to the cytosol due to activity of chloride channels) [8]. Some cells can capture H_2O_2 from the extracellular space due to the activity of aquaporins (known in this context as peroxyporins), particularly AQP8 [8, 9] (Fig. 2).

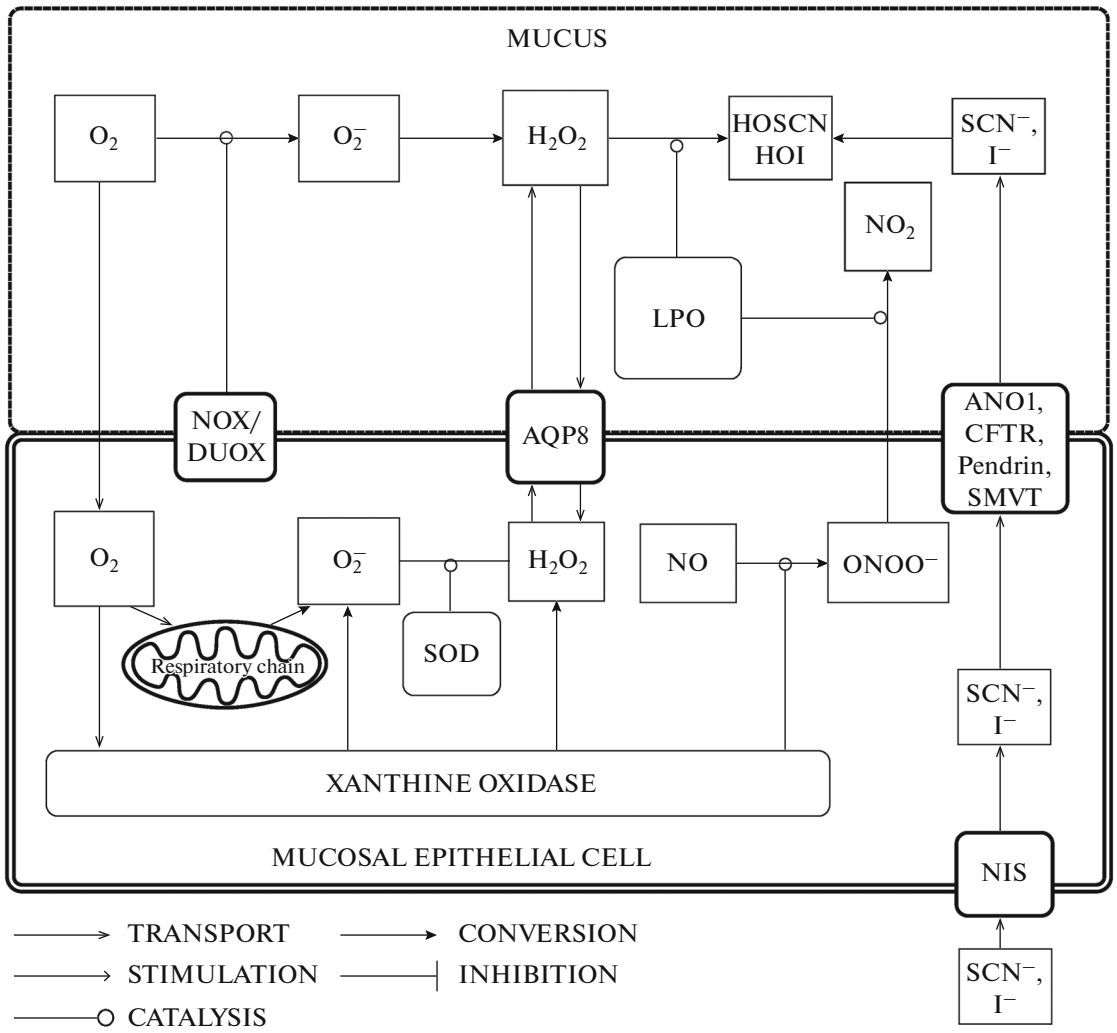

Fig. 2. Formation and conversion of intracellular and extracellular pools of hydrogen peroxide, providing production of hypothiocyanate and hypoiodite on the surface of epithelial cells of the respiratory tract mucosa. SOD, superoxide dismutase; LPO, lactoperoxidase; NIS, sodium iodide symporter.

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_2O_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 Th_2 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

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 H_2O_2 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 H_2O_2 (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 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 hypoiodite (OI^-) through I_2 as the intermediate product. OI^- and I_2 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 (T_4) delivered to these cells; T_4 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 SCN_2, 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—NADP) [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 H_2O_2 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 NO_3 to NO_2, being functionally coupled with xanthine oxidase, which generates O_2^- and hydrogen peroxide [34], it can be assumed that, in addition to

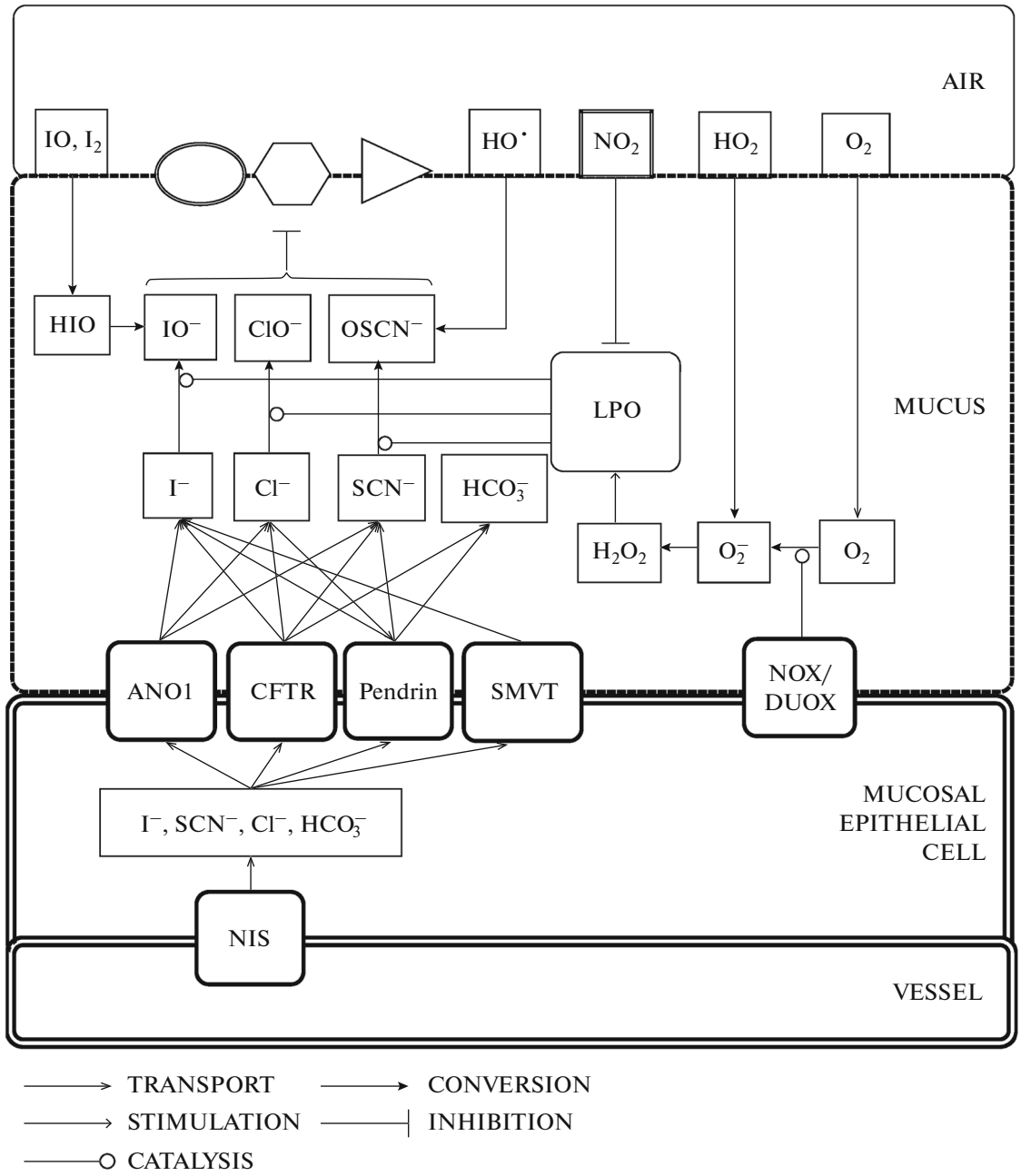

Fig. 3. Transport and enzymatic systems of bronchial tree epithelial cells that form lactoperoxidase-dependent nonspecific defense mechanisms.

DUOX, xanthine oxidase can play the role of a H_2O_2 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 NO_3^- 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 O_2^- to hydrogen peroxide lead to LPO-dependent generation of hypothiocyanate and hypoiodite, which have various biological effects.

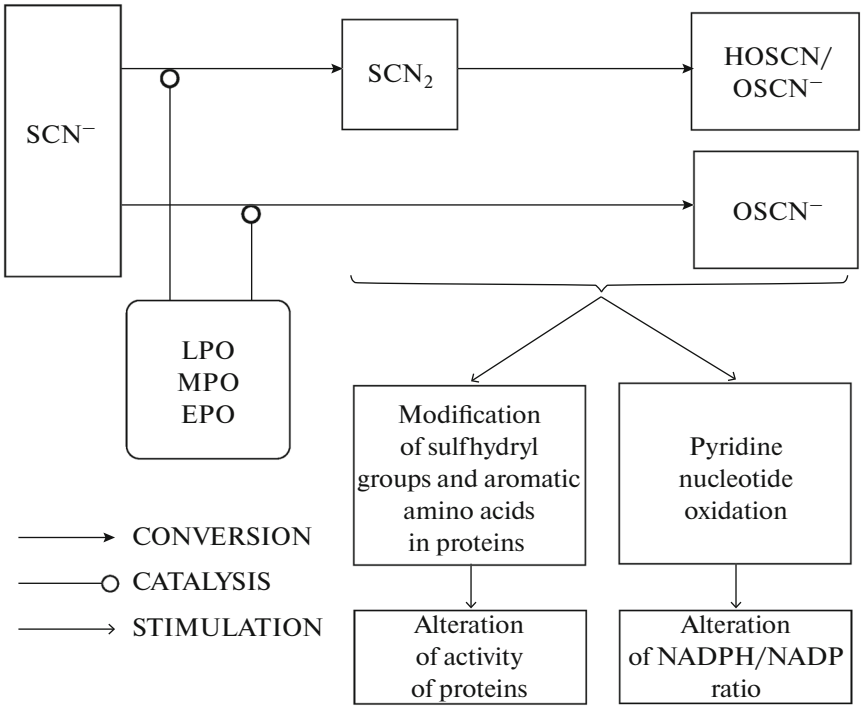

Fig. 4. Production of thiocyanate derivatives by peroxidases causing modification of cellular proteins and a change in the ratio of reduced and oxidized pyridine nucleotides. LPO—lactoperoxidase, MPO—myeloperoxidase, EPO—eosinophilic peroxidase.

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 IC_{50} 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-

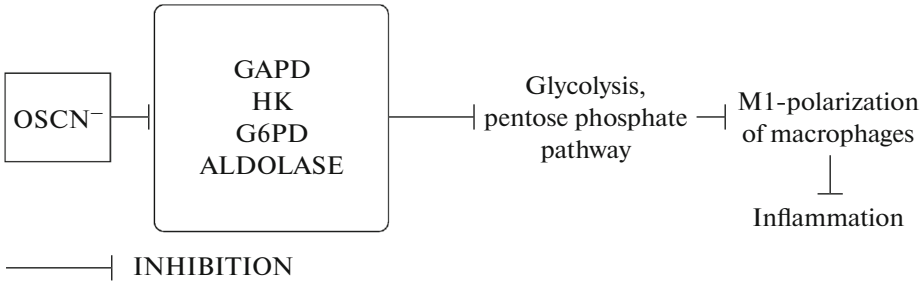

Fig. 5. Probable mechanism of the anti-inflammatory action of hypothiocyanate $OSCN^-$, associated with suppression of the activity of glycolytic and the pentose phosphate pathway enzymes (GAPDv—glyceraldehyde-3-phosphate dehydrogenase, HK—hexokinase, G6PD—glucose-6-phosphate dehydrogenase, aldolase) and M1-polarization of tissue macrophages.

rus or RSV, the use of an alternative substrate (iodide) caused the activation of DUOX/LPO in the context of generation of a substance (HOI) possessing a pronounced virucidal effect against encapsidated and enveloped respiratory viruses [41].

Good evidence exists that the oxidizing ability of hypothiocyanate underlies its antibacterial and antiviral effects, while hydrogen peroxide has low antibacterial activity [11, 42]. For example, a high antiviral activity of hypothiocyanate, produced by LPO from thiocyanate, was shown against a number of influenza viruses under cell-free conditions [31], which quite fully mimicked the processes occurring in the mucosal layer of the lung epithelium [43]. It has been demonstrated that hypothiocyanate (but not H_2O_2) formed in bronchial tree epithelial cells stimulates the dimerization of protein kinase A (PKA), which increases the activity of the transcription factor NF-κB, which ensures expression of genes encoding peptides with pro-inflammatory activity, including interleukins; however, hypothiocyanate, acting at high concentrations, causes the development of necrosis [44]. Such mechanism may be relevant in the context of bronchial asthma pathogenesis and researchers proposed to use of heme peroxidase inhibitors (which are used in the treatment of hyperthyroidism) as new therapeutic agents for bronchial asthma [45].

In the presence of 400 μM SCN^- in the incubation medium of bronchial epithelial cells with actively working LPO there was a pronounced bactericidal effect in vitro [21]. Under similar conditions the presence of low concentration of iodide (5 μM) resulted in a virucidal effect in vitro [21, 41]. It should be taken into consideration that, most likely, hypothiocyanate and hypoiodite compete for common transport and enzyme systems, and this affects the interpretation of data on their biological activity.

Interestingly, in cystic fibrosis SCN^- transport to the mucosal surface is reduced due to aberrant CFTR activity, which hinders the hypothiocyanate generation [22, 33], and an increase in the thiocyanate level in these patients is associated with an improvement in lung function [18]. 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 hypothiocyanate 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 hypothiocyanate (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 hypothiocyanate 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, hypothiocyanate 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:

$$O_2^- + H_2O \Leftrightarrow HO_2^\bullet + OH^-.$$

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 $HO_2^\bullet/O_2^-$ is converted to hydrogen peroxide in 1 h:

$$HO_2^\bullet + HO_2^\bullet \rightarrow H_2O_2 + O_2,$$

$$HO_2^\bullet + O_2^- + H_2O \rightarrow H_2O_2 + O_2 + OH^-.$$

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 hypothiocyanate in the respiratory tract was previously proven in a patent [60].

The non-enzymatic mechanism of formation of hypothiocyanate 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]:

$$SCN^- + 2HO^\bullet \rightarrow OSCN^- + H_2O,$$

$$OSCN^- + SCN^- + H_2O \rightarrow (SCN)_2 + 2OH^-.$$

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.

$$CH_2I_2 + h\nu \rightarrow CH_2 + 2I,$$

$$CH_2IBr + h\nu \rightarrow CH_2 + I + Br,$$

$$I_2 + h\nu \rightarrow 2I.$$

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

$$I + O_3 \rightarrow IO + O_2,$$

$$IO + HO_2 \rightarrow HOI + O_2.$$

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

$$HIO \rightarrow H^+ + IO^-.$$

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

$$I_{2(aq)} + H_2O \rightarrow HIO + HI.$$

Besides the above mentioned iodine compounds, iodite ion I^-, 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

iodic acid [67]. 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 iodous 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_2^- 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_2O_2 system is more pronounced in NaI—$\log(TCID_{50}/mL) = 0.7 \pm 0.1$—at an initial level of 5.2 ± 0.07 than for NaBr—$\log(TCID_{50}/mL) = 1.1 \pm 0.88$—and even more than in NaCl—$\log(TCID_{50}/mL) = 5.0 \pm 0.19$. However, in the MPO/$H_2O_2$ system, the antiviral activity of NaCl—$\log(TCID_{50}/mL) = 1.2 \pm 0.22$—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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COMPLIANCE WITH ETHICAL STANDARDS

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

REFERENCES

1. Ware, H.H., Kulkarni, V.V., Wang, Y., Pantaleón García, J., Leiva Juarez, M., Kirkpatrick, C.T., Wali, S., Syed, S., Kontoyiannis, A.D., Sikkema, W.K.A., Tour, J.M., and Evans, S.E., *PLoS One*, 2019, vol. 14, no. 2, e0208216. https://doi.org/10.1371/journal.pone.0208216
2. Baulig, A., Garlatti, M., Bonvallot, V., Marchand, A., Barouki, R., Marano, F., and Baeza-Squiban, A., *Am. J. Physiol. Lung Cell. Mol. Physiol.*, 2003, vol. 285, no. 3, pp. L671–L679. https://doi.org/10.1152/ajplung.00419.2002
3. Kirkpatrick, C.T., Wang, Y., Leiva Juarez, M.M., Shivshankar, P., Pantaleón García, J., Plumer, A.K., Kulkarni, V.V., Ware, H.H., Gulraiz, F., Chavez Cavasos, M.A., Martinez Zayas, G., Wali, S., Rice, A.P., Liu, H., Tour, J.M., Sikkema, W.K.A., Cruz Solbes, A.S., Youker, K.A., Tuvim, M.J., Dickey, B.F., and Evans, S.E., *mBio*, 2018, vol. 9, no. 3, e00696-18. https://doi.org/10.1128/mBio.00696-18
4. Amatore, D., Sgarbanti, R., Aquilano, K., Baldelli, S., Limongi, D., Civitelli, L., Nencioni, L., Garaci, E., Ciriolo, M.R., and Palamara, A.T., *Cell Microbiol.*, 2015, vol. 17, no. 1, pp. 131–145. https://doi.org/10.1111/cmi.12343
5. Chen, K.K., Minakuchi, M., Wuputra, K., Ku, C.C., Pan, J.B., Kuo, K.K., Lin, Y.C., Saito, S., Lin, C.S., and Yokoyama, K.K., *BMC Microbiol.*, 2020, vol. 20, no. 1, 214. https://doi.org/10.1186/s12866-020-01890-9
6. Konno, T., Melo, E.P., Chambers, J.E., and Avezov, E., *Cells*, 2021, vol. 10, no. 2, 233. https://doi.org/10.3390/cells10020233
7. Checa, J. and Aran, J.M., *J. Inflamm. Res.*, 2020, vol. 13, 1057. https://doi.org/10.2147/JIR.S275595
8. Lennicke, C., Rahn, J., Lichtenfels, R., Wessjohann, L.A., and Seliger, B., *Cell Commun. Signal.*, 2015, vol. 13, no. 1, 39. https://doi.org/10.1186/s12964-015-0118-6
9. Buck, T., Hack, C.T., Berg, D., Berg, U., Kunz, L., and Mayerhofer, A., *Sci. Rep.*, 2019, vol. 9, no. 1, 3585. https://doi.org/10.1038/s41598-019-40329-8
10. Conner, G.E., Salathe, M., and Forteza, R., *Am. J. Respir. Crit. Care Med.*, 2002, vol. 166, Supplement 1, pp. S57–S61. https://doi.org/10.1164/rccm.2206018
11. Sarr, D., Tóth, E., Gingerich, A., and Rada, B., *J. Microbiol.*, 2018, vol. 56, no. 6, pp. 373–386. https://doi.org/10.1007/s12275-018-7545-1
12. Lambeth, J.D., *Nature Rev. Immunol.*, 2004, vol. 4, no. 3, pp. 181–189. https://doi.org/10.1038/nri1312
13. van der Vliet, A., Danyal, K., and Heppner, D.E., *Br. J. Pharmacol.*, 2018, vol. 175, no. 9, pp. 1401–1418. https://doi.org/10.1111/bph.14158
14. Fischer, H., Gonzales, L.K., Kolla, V., Schwarzer, C., Miot, F., Illek, B., and Ballard, P.L., *Am. J. Physiol. Lung Cell. Mol. Physiol.*, 2007, vol. 292, no. 6, L1506–L1514. https://doi.org/10.1152/ajplung.00029.2007
15. Derscheid, R.J., van Geelen, A., Berkebile, A.R., Gallup, J.M., Hostetter, S.J., Banfi, B., McCray, P.B., Jr., and Ackermann, M.R., *Am. J. Respir. Cell Mol. Biol.*, 2014, vol. 50, no. 2, pp. 389–397. https://doi.org/10.1165/rcmb.2012-0529OC
16. Chandler, J.D. and Day, B.J., *Biochem. Pharmacol.*, 2012, vol. 84, no. 11, pp. 1381–1387. https://doi.org/10.1016/j.bcp.2012.07.029
17. Fischer, H., *Antioxid. Redox Signal.*, 2009, vol. 11, pp. 2453–2465. https://doi.org/10.1089/ars.2009.2558
18. Chandler, J.D., Horati, H., Walker, D.I., Pagliano, E., Tirouvanziam, R., Veltman, M., Scholte, B.J., Janssens, H.M., Go, Y.-M., and Jones, D.P., *Free Radic. Biol. Med.*, 2018, vol. 126, pp. 334–340. https://doi.org/10.1016/j.freeradbiomed.2018.08.012
19. Tonoyan, L., Fleming, G.T.A., Mc Cay, P.H., Friel, R., and O'Flaherty, V., *Front. Microbiol.*, 2017, vol. 8, p. 680. https://doi.org/10.3389/fmicb.2017.00680
20. Barca-Mayo, O., Liao, X.-H., DiCosmo, C., Dumitrescu, A., Moreno-Vinasco, L., Wade, M.S., Sammani, S., Mirzapoiazova, T., Garcia, J.G.N., Refetoff, S., and Weiss, R.E., *Proc. Nat. Acad. Sci. USA*, 2011, vol. 108, no. 49, pp. E1321–E1329. https://doi.org/10.1073/pnas.1109926108
21. Portulano, C., Paroder-Belenitsky, M., and Carrasco, N., *Endocrine Rev.*, 2014, vol. 35, no. 1, pp. 106–149. https://doi.org/10.1210/er.2012-1036
22. Fragoso, M.A., Fernandez, V., Forteza, R., Randell, S.H., Salathe, M., and Conner, G.E., *J. Physiol.*, 2004, vol. 561, pt 1, pp. 183–194. https://doi.org/10.1113/jphysiol.2004.071548
23. Vieja, A.D.L. and Santisteban, P., *Endocrine-Related Cancer*, 2018, vol. 25, no. 4, R225. https://doi.org/10.1530/erc-17-0515
24. Yoshida, A., Hisatome, I., Taniguchi, S., Sasaki, N., Yamamoto, Y., Miake, J., Fukui, H., Shimizu, H., Okamura, T., Okura, T., Igawa, O., Shigemasa, C., Green, E.D., Kohn, L.D., and Suzuki, K., *Endocrinology*, 2004, vol. 145, no. 9, pp. 4301–4308. https://doi.org/10.1210/en.2004-0048
25. Klebanoff, S.J., *J. Leukoc. Biol.*, 2005, vol. 77, no. 5, pp. 598–625. https://doi.org/10.1189/jlb.1204697
26. Chen, S., Chen, H., Du, Q., and Shen, J., *Front. Physiol.*, 2020, vol. 11, 433. https://doi.org/10.3389/fphys.2020.00433
27. Sokolov, A.V., Kostevich, V.A., Gorbunov, N.P., Grigorieva, D.V., Gorudko, I.V., Vasilyev, V.B., and Panasenko, O.M., *Medical Immunology* (Russia), 2018, vol. 20, no. 5, pp. 699–710. https://doi.org/10.15789/1563-0625-2018-5-699-710
28. Tonoyan, L., Montagner, D., Friel, R., and O'Flaherty, V., *Biochem. Pharmacol.*, 2020, vol. 182, 114281. https://doi.org/10.1016/j.bcp.2020.114281
29. Gau, J., Furtmüller, P.-G., Obinger, C., Arnhold, J., and Flemmig, J., *Biochem. Biophys. Rep.*, 2015, vol. 4, pp. 257–267. https://doi.org/10.1016/j.bbrep.2015.10.001

30. Gerson, C., Sabater, J., Scuri, M., Torbati, A., Coffey, R., Abraham, J.W., Lauredo, I., Forteza, R., Wanner, A., Salathe, M., Abraham, W.M., and Conner, G.E., *Am. J. Respir. Cell Mol. Biol.*, 2000, vol. 22, no. 6, pp. 665–671. https://doi.org/10.1165/ajrcmb.22.6.3980

31. Patel, U., Gingerich, A., Widman, L., Sarr, D., Tripp, R.A., and Rada, B., *PLoS One*, 2018, vol. 13, no. 7, e0199167. https://doi.org/10.1371/journal.pone.0199167

32. Gingerich, A.D., Doja, F., Thomason, R., Tóth, E., Bradshaw, J.L., Douglass, M.V., McDaniel, L.S., and Rada, B., *PLoS One*, 2020, vol. 15, no. 7, e0236389. https://doi.org/10.1371/journal.pone.0236389

33. Wijkstrom-Frei, C., El-Chemaly, S., Ali-Rachedi, R., Gerson, C., Cobas, M.A., Forteza, R., Salathe, M., and Conner, G.E., *Am. J. Respir. Cell Mol. Biol.*, 2003, vol. 29, no.2, pp. 206–212. https://doi.org/10.1165/rcmb.2002-0152OC

34. Silanikove, N., Shapiro, F., Shamay, A., and Leitner, G., *Free Radic. Biol. Med.*, 2005, vol. 38, no. 9, pp. 1139–1151. https://doi.org/10.1016/j.freeradbiomed.2004.12.011

35. Schönfeld, P., Montero, L., and Fabian, J., *Biophys. J.*, 2005, vol. 89, no. 3, pp. 1504–1515. https://doi.org/10.1529/biophysj.105.059006

36. Hawkins, C.L. *Free Radical Res.*, 2009, vol. 43, no. 12, pp. 1147–1158. https://doi.org/10.3109/10715760903214462

37. Soto-Heredero, G., Gomez de las Heras, M.M., Gabandé-Rodríguez, E., Oller, J., and Mittelbrunn, M., *FEBS J.*, 2020, vol. 287, no. 16, pp. 3350–3369.

38. Cegolon, L., Salata, C., Piccoli, E., Juarez, V., Palu, G., Mastrangelo, G., and Calistri, A., *Int. J. Hyg. Environ. Health*, 2014, vol. 217, no. 1, pp. 17–22. https://doi.org/10.1016/j.ijheh.2013.03.001

39. Cegolon, L., *Int. J. Hyg. Environ. Health*, 2020, vol. 227, 113520. https://doi.org/10.1016/j.ijheh.2020.113520

40. Mikola, H., Waris, M., and Tenovuo, J., *Antiviral Res.*, 1995, vol. 26, no. 2, pp. 161–171. https://doi.org/10.1016/0166-3542(94)00073-H

41. Fischer, A.J., Lennemann, N.J., Krishnamurthy, S., Pócza, P., Durairaj, L., Launspach, J.L., Rhein, B.A., Wohlford-Lenane, C., Lorentzen, D., Bánfi, B., and McCray, P.B., Jr., *Am. J. Respir. Cell Mol. Biol.*, 2011, vol. 45, no. 4, pp. 874–881. https://doi.org/10.1165/rcmb.2010-0329OC

42. Grandvaux, N., Mariani, M., and Fink, K., *Clin. Sci.*, 2014, vol. 128, no. 6, pp. 337–347. https://doi.org/10.1042/cs20140321

43. Leto, T.L. and Rada, B., in *National Institute of Allergy and Infectious Diseases, NIH*: vol. 3: *Intramural Research*, Georgiev, V.St., Ed., Springer, 2010, pp. 311–318. https://doi.org/10.1007/978-1-60761-512-5_33

44. Suzuki, S., Ogawa, M., Ohta, S., Nunomura, S., Nanri, Y., Shiraishi, H., Mitamura, Y., Yoshihara, T., Lee, J.J., and Izuhara, K., *J. Biol. Chem.*, 2016, vol. 291, no. 53, pp. 27219–27227. https://doi.org/10.1074/jbc.M116.746909

45. Izuhara, K., Suzuki, S., Ogawa, M., Nunomura, S., Nanri, Y., Mitamura, Y., and Yoshihara, T., *Oxid. Med. Cell Longev.*, 2017, vol. 2017, 1054801. https://doi.org/10.1155/2017/1054801

46. Scanlon, K.M., Gau, Y., Zhu, J., Skerry, C., Wall, S.M., Soleimani, M., and Carbonetti, N.H., *Infect. Immun.*, 2014, vol. 82, no. 10, pp. 4212–4221. https://doi.org/10.1128/iai.02222-14

47. Shi, S., Pang, C., Guo, S., Chen, Y., Ma, B., Qu, C., Ji, Q., and An, H., *Comput. Struct. Biotechnol. J.*, 2020, vol. 18, pp. 714–722. https://doi.org/10.1016/j.csbj.2020.03.015

48. Gorrieri, G., Scudieri, P., Caci, E., Schiavon, M., Tomati, V., Sirci, F., Napolitano, F., Carrella, D., Gianotti, A., Musante, I., Favia, M., Casavola, V., Guerra, L., Rea, F., Ravazzolo, R., di Bernardo, D., and Galietta, L., *Sci. Rep.*, 2016, vol. 6, 36016. https://doi.org/10.1038/srep36016

49. Lin, J., Jiang, Y., Li, L., Liu, Y., Tang, H., and Jiang, D., *Exp. Cell Res.*, 2015, vol. 334, no. 2, pp. 260–269. https://doi.org/10.1016/j.yexcr.2015.02.026

50. Quick, M. and Shi, L., *Vitamins Hormones*, 2015, vol. 98, pp. 63–100. https://doi.org/10.1016/bs.vh.2014.12.003

51. Royaux, I.E., Suzuki, K., Mori, A., Katoh, R., Everett, L.A., Kohn, L.D., and Green, E.D., *Endocrinology*, 2000, vol. 141, no. 2, pp. 839–845. https://doi.org/10.1210/endo.141.2.7303

52. Nofziger, C., Dossena, S., Suzuki, S., Izuhara, K., and Paulmichl, M., *Cell Physiol. Biochem.*, 2011, vol. 28, no. 3, pp. 571–578. https://doi.org/10.1159/000335115

53. Allahverdian, S., Harada, N., Singhera, G.K., Knight, D.A., and Dorscheid, D.R., *Am. J. Respir. Cell Mol. Biol.*, 2008, vol. 38, no. 2, pp. 153–160. https://doi.org/10.1165/rcmb.2007-0173OC

54. Pahl, A., Zhang, M., Kuss, H., Szelenyi, I., and Brune, K., *Br. J. Pharmacol.*, 2002, vol. 135, no. 8, pp. 1915–1926. https://doi.org/10.1038/sj.bjp.0704656

55. Seibold, M.A., *Ann. Am. Thorac. Soc.*, 2018, vol. 15, Suppl. 2, pp. S98–S102. https://doi.org/10.1513/AnnalsATS.201711-868MG

56. Vatrella, A., Fabozzi, I., Calabrese, C., Maselli, R., and Pelaia, G., *J. Asthma Allergy*, 2014, vol. 7, pp. 123–130. https://doi.org/10.2147/jaa.s52387

57. Turkia, M., *SSRN Electronic J.*, 2020, vol. 2020, 3604987. https://doi.org/10.2139/ssrn.3604987

58. Whalley, L.K., Furneaux, K.L., Goddard, A., Lee, J.D., Mahajan, A., Oetjen, H., Read, K.A., Kaaden, N., Carpenter, L.J., Lewis, A.C., Plane, J.M.C., Saltzman, E.S., Wiedensohler, A., and Heard, D.E., *Atmos. Chem. Phys.*, 2010, vol. 10, no. 4, pp. 1555–1576. https://doi.org/10.5194/acp-10-1555-2010

59. Cory, R.M., Davis, T.W., Dick, G.J., Johengen, T., Denef, V.J., Berry, M.A., Page, S.E., Watson, S.B., Yuhas, K., and Kling, G.W., *Front. Marine Sci.*, 2016, vol. 3, 54. https://doi.org/10.3389/fmars.2016.00054

60. Lee, J.D., in *Methods for Improving Respiratory System Health and Increasing the Concentration of Hypothiocyanate Ion in Vertebrate Lungs*, US 2019/0336526 A1. 2019.

61. Viña Mediavilla, J.J., Fernandez Perez, B., Fernandez de Cordoba, M.C., Ayala Espina, J., Ania, C.O., *Molecules*, 2019, vol. 24, no. 7, 1373. https://doi.org/10.3390/molecules24071373

62. Saiz-Lopez, A., Plane, J.M.C., Baker, A.R., Carpenter, L.J., von Glasow, R., Gómez Martín, J.C., McFiggans, G., and Saunders, R.W., *Chemical Rev*., 2012, vol. 112, no. 3, pp. 1773–1804. https://doi.org/10.1021/cr200029u

63. Schönhardt, A., Richter, A., Wittrock, F., Kirk, H., Oetjen, H., Roscoe, H.K., and Burrows, J.P., *Atmos. Chem. Phys*., 2008, vol. 8, no. 3, pp. 637–653. https://doi.org/10.5194/acp-8-637-2008

64. Bichsel, Y. and von Gunten, U., *Envir. Sci. Technol*., 1999, vol. 33, no. 22, pp. 4040–4045. https://doi.org/10.1021/es990336c

65. Allen, T.L. and Keefer, R.M., *J. Am. Chem. Soc*., 1955, vol. 77, no. 11, pp. 2957–2960. https://doi.org/10.1021/ja01616a008

66. Hove, P.R., Mobley, D., Magunda, F., and Call, D.R., *Int. J. Environ. Res. Public Health*, 2020, vol. 17, no. 10, 3489. https://doi.org/10.3390/ijerph17103489

67. Eggers, M., *Infect. Dis. Ther*., 2019, vol. 8, no. 4, pp. 581–593. https://doi.org/10.1007/s40121-019-00260-x

68. Eggers, M., Koburger-Janssen, T., Eickmann, M., and Zorn, J., *Infect. Dis. Ther*., 2018, vol. 7, no. 2, pp. 249–259. https://doi.org/10.1007/s40121-018-0200-7

69. Fischer, H, and Widdicombe, J.H., *J. Membrane Biol*., 2006, vol. 211, no. 3, pp. 139–150. https://doi.org/10.1007/s00232-006-0861-0

70. Ferrari, R.P., Ghibaudi, E.M., Traversa, S., Laurenti, E., de Gioia, L., and Salmona, M., *J. Inorg. Biochem*., 1997, vol. 68, no. 1, pp. 17–26. https://doi.org/10.1016/S0162-0134(97)00003-2

71. Belding, M.E., Klebanoff, S.J., and Ray, C.G., *Science*, 1970, vol. 167, no. 3915, pp. 195–196. https://doi.org/10.1126/science.167.3915.195

72. Ogen, Y., *Sci. Total Envir*., 2020, vol. 726, 138605. https://doi.org/10.1016/j.scitotenv.2020.138605

73. Travaglio, M., Yu, Y., Popovic, R., Selley, L., Leal, N.S., and Martins, L.M., *Environ. Pollut*., 2021, vol. 268, 115859. https://doi.org/10.1016/j.envpol.2020.115859

74. Konstantinoudis, G., Padellini, T., Bennett, J., Davies, B., Ezzati, M., and Blangiardo, M., *Environ. Int*., 2021, vol. 146, 106316. https://doi.org/10.1016/j.envint.2020.106316

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