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Altered Expression Profile of Superoxide Dismutase Isoforms in Nasal Polyps from Nonallergic Patients

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***Objective/Hypothesis:* Nasal polyposis (NP) is a chronic inflammatory disease of the upper respiratory tract. The pathophysiology is unknown but has been shown to be multifactorial. Free radical-mediated damage has been implicated in the pathogenesis of NP. Superoxide dismutases (SODs) are the first and the most important line of antioxidant enzyme defense against reactive oxygen species. Moreover, isozymes of the SOD family are critical for modulating the activity of nitric oxide, a gaseous free radical that is believed to play roles in the physiology and pathology of respiratory tracts. However, the expression profile of SOD isoforms in NP remains unclear. We aimed to investigate the expression profile of the SOD isoforms in nasal polyps from nonallergic patients. *Study Design:* Prospective study. *Methods:* Nasal polyp tissues were obtained from eight nonallergic patients who underwent elective polypectomy; mucosal specimens from the middle turbinates were acquired from eight subjects without NP as control tissues. The expression profile of SOD isoenzymes, SOD1, SOD2, and SOD3, in the nasal tissues was determined by reverse transcription-polymerase chain reaction (RT-PCR), enzyme-linked immunosorbent assay (ELISA), and Western blotting (WB). *Results:* NP in all eight of the NP patients manifested as severe or recurrent sinonasal polyposis clinically. The expression pattern of SOD isoenzymes evaluated by RT-PCR analysis indicated that the mean levels of SOD1 mRNA and, to a greater extent, SOD3 mRNA were higher in polyp tissues than in control tissues. There was no significant difference in the expression levels of SOD2 mRNA between the two groups. The data from ELISA and WB analysis showed that there were increased expressions of SOD1 and SOD3 protein in polyp tissues compared with the control tissues, but there was no difference in the expression of SOD2 protein between the two groups. The results from RT-PCR, ELISA, and WB were paralleled and revealed that the expressions of SOD1 and, to a greater extent, SOD3 were higher in polyp tissues than in the control group. *Conclusions:* The expressions of SOD3 and SOD1 were higher in polyp tissues. These results are consistent with previously reported data and support the hypothesis that there is increased oxidative stress in NP. Our data also suggest that the SODs might be important in the pathogenesis of NP; however, the roles these SOD isoforms, especially SOD3, play in both normal nasal mucosa and NP require further clarification. *Key Words:* Free radical, nasal polyps, nitric oxide, oxidative stress, peroxynitrite, polyclonal antihuman SOD3 antiserum, superoxide dismutase isoenzymes.**

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INTRODUCTION

Chronic rhinosinusitis affects up to 30 million Americans annually and has been estimated to incur 2.4 billion dollars in medical costs per year. Nasal polyposis (NP) is the most severe manifestation of sinusitis, and is the ultimate manifestation of chronic inflammation.[1] In the general population, the overall prevalence rate ranges from 1% to 4%.[2] NP usually presents with nasal obstruction, increased secretion, loss of smell, headache, and recurrent respiratory infection; it is also known to aggravate asthma severity.[2] Unfortunately, treatment of severe sinonasal polyposis still remains unsatisfactory, with a high recurrence rate.[1,2] The pathophysiology is unknown but

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has been shown to be multifactorial; experimental models have indicated that chronic inflammation appears to be required.[2]

Free radical (FR)-mediated damage has been implicated in the pathogenesis of several disease processes, including arthritis, atherosclerosis,[3] as well as nasal polyps.[4–6] Several studies have noted that histopathologic abnormalities of NP, such as epithelial damage, edema and inflammation, were closely related to the infiltration of inflammatory cells.[2,4] Airway inflammatory cells are the likely source; inflammatory cells produce FRs during phagocytosis, which is the major source of biological reactive oxygen species (ROS, e.g., O_2^-, H_2O_2 and OH·).[3,7,8] Resultant FR damage to lipid (peroxidation), protein, and DNA leads to various forms of cell injury. Recent studies have reported high levels of malondialdehyde (MDA) in NP tissue, which represents an increase in FR; this evidence supports the existence of cell injury in NP tissue.[4,5]

Many diseases are linked to damage from ROS as a result of an imbalance between ROS and scavenging systems (antioxidants), a condition called oxidant/antioxidant imbalance or oxidative stress. The superoxide dismutases (SODs) are the first and the most important line of antioxidant enzyme defense against ROS.[3,9] The SOD family is composed of three metalloenzymes, SOD1, SOD2, and SOD3, that catalyze the dismutation of superoxide anion (O_2^-). SOD1 (CuZn-SOD) is a homodimeric cytosolic CuZn enzyme; it has a molecular mass of 32 kD. SOD2 (manganese [Mn]-SOD), unlike SOD1, is a 23 KDa homotetrameric enzyme that functions in the mitochondria; it has Mn as a cofactor.[3,9] SOD3 (extracellular [EC]-SOD) is the most recently discovered and last characterized member of this family. When synthesized, it contains a signal peptide that directs this enzyme exclusively to EC spaces. The enzyme exists as a homotetramer (135 kD) with high affinity for heparin.[3,9]

The isozymes of the SOD family are critical in modulating the activity of nitric oxide (NO), a gaseous FR which is believed to play roles in the physiology and pathology of respiratory tracts. NO, an important regulator of biological functions, is known to be produced from various types of cells and tissues in response to inflammatory stimulation.[7,8,10] Exhaled breath contains considerable amounts of NO produced mainly by the upper airway surface cells; the lower respiratory tract and lungs appear to make only a minor contribution.[10,11] Several biological roles of nasal NO in the upper airway are speculated such as protection from infections as part of the host defense, mediators of proinflammatory and anti-inflammatory effects, and regulators of mucociliary clearance.[7,8,10] Clinical evidence has clearly shown that the concentration of NO in exhaled air is increased in patients with airway inflammations including asthma and allergic rhinitis; however, contrary with these two comorbidities, NO levels were low in NP, although the levels of inducible NO synthase (iNOS) remained high.[8,10,11] NO rapidly reacts with superoxide to produce very reactive and toxic peroxynitrite ($ONOO^-$), which was shown to play roles in inflammatory diseases.[6–8,10] Using nitrotyrosine immunohistochemical staining, Ruffoli et al.[6] suggested that there exists progressive epithelium injury in polyp tissues caused by peroxynitrite. In addition to the toxic effect, this reaction might decrease the concentration of NO, thereby diminishing its bioavailability.[8]

The significance of oxidative stress and NO activity in the pathophysiology of inflammatory respiratory diseases have been recognized, especially in the lower airway of patients with asthma.[8] SOD isoforms are important in both oxidative stress and NO activity; however, the expression profiles of SOD isoforms remain unclear in NP, a common chronic inflammatory disease of the upper airway. Although NP and asthma share similar pathophysiology, there are differences between the upper and lower airways. We aimed to investigate the expression profile of the SOD isoforms in nasal polyps from nonallergic patients.

MATERIALS AND METHODS

Patient Selection

This study involved 16 patients recruited from the Department of Otolaryngology, China Medical University Hospital (CMUH), Taichung, Taiwan. Polyp specimens were obtained from eight patients with NP when they underwent endoscopic sinus surgery. Control specimens (lateral lamella of middle turbinate) were acquired from eight patients without NP when they underwent endoscopic sinus surgery for correction of anatomic variation, such as concha bullosa. Bilateral NP was diagnosed based on history, anterior rhinoscopy, nasal endoscopy, and sinus computed tomography (CT) scan. NP was defined as the presence of endoscopically visible bilateral polyps growing from the middle meatus into the nasal cavities and affecting more than one sinus according to CT scan.[1] Endoscopy findings were scored according to the method by Lund and Kennedy.[12] The following parameters were graded: presence or absence and extent of nasal polyps, edema, discharge, crusting, and scaring. For nasal polyps, 0 was given for the absence of polyps, 1 for polyps present within the middle meatus, and 2 for polyps beyond the middle meatus. Under the definition of NP, all NP patients in this study were shown to have an endoscopic grading of 2 for NP (Table I). Findings on sinus coronal CT scans were graded using the Lund-Mackay CT scoring system.[12] Allergic status was evaluated based on the measurement of serum total immunoglobulin Ig)E and an allergy screening test (Phadiatop, Pharmacia CAP system, Uppsala, Sweden) comprising a panel of 23 aeroallergens prevalent throughout Taiwan, including five trees, five grasses, five weeds, four molds, dander from three animal species, and one species of mite (*Dermatophagoides pteronissinus*). Subjects were considered nonatopic if they did not have Phadiatop positivity and had a serum IgE level less than 100 IU/mL. None of the enrolled patients and controls could have any seasonal or perennial allergic symptoms at the time allergic status evaluation.[13] Moreover, none of the study subjects exhibited symptoms of common cold, and none of them had taken any form of antibiotics, antihistamines, or corticosteroids for at least 4 weeks before sampling. There were no differences between the two groups in sex and age, smoking, and alcohol consumption ($P > .05$). The study protocol was approved by the institutional review board of the CMUH, and informed consent was obtained from all subjects.

Reverse-Transcription Polymerase Chain Reaction of SOD Isoenzymes

All of the tissue samples were immediately frozen in liquid nitrogen for less than 10 minute after excision and kept until analysis. The expression levels of SOD isoenzymes mRNA were evaluated by reverse transcription-polymerase chain reaction

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TABLE I.
Demographic Information for Patients with Nasal Polyps.

Patient	Age (yr)	Sex (M/F)	Endoscopy Score for Polyp*	CT Score†	Prior Sinus Surgery	Aspirin Sensitivity	Asthma	Phadiatop	Total IgE
A	42	M	2	17	Yes	No	No	Negative	1.2
B	30	M	2	15	No	No	No	Negative	86.6
C	23	F	2	12	No	No	No	Negative	33.5
D	52	M	2	10	Yes	No	Yes	Negative	49.4
E	68	F	2	12	No	No	Yes	Negative	15.1
F	54	F	2	18	Yes	Yes	Yes	Negative	28.3
G	27	M	2	16	No	No	No	Negative	15.6
H	38	M	2	14	No	No	No	Negative	37.7

*Endoscopic grading for the presence of nasal polyps according to Lund and Kennedy. †Lund-Mackay computed tomography (CT) staging system. Ig = immunoglobulin.

(RT-PCR). Total RNA was isolated from nasal polyp tissues and control tissues using TRIzol reagent (Gibco BRL, Gaithersburg, MD) according to the manufacturer's instructions. Isolated RNA was dissolved in diethylpyrocarbonate-treated H_2O, and the concentration and purity were measured . Five micrograms of total RNA were reversely transcribed into cDNA using Moloney murine leukemia virus-RT and oligo dT primers (Promega, Madison, WI). cDNA was stored at –20°C until examination. The PCR mixture consisted of 1.0 μL (approximately 0.25 μg) of sample cDNA solution, 5.0 μL of Mg^{2+}, 5.0 μL of 10× PCR buffer (Promega), 4.0 μL (2.5 5mol/L each) of dNTP mixture (Promega), 2.0 μL (10.0 0mol/L) of forward and reverse primers, 0.1 μL of Tag DNA polymerase (Promega), and distilled water to give a final volume of 50.0 μL. All PCR amplifications were directed by specific primers as listed in Table II. Amplification was performed in a thermocycler as follows: 5 minutes at 94°C, followed by 35 cycles for 30 seconds at 94°C, 30 seconds at 57°C, and 30 seconds at 62°C. After cycling, there was a DNA elongation period of 7 minutes at 72°C. The PCR products were separated on 1.5% agarose gels containing 1 μg/mL ethidium bromide and photographed under ultraviolet illumination (Fig 1A). The size of each PCR product was established from the migration of the DNA size marker that ran concurrently (100 bp DNA marker). PCR amplification of β-actin was used as a loading control. The intensity of each PCR-amplified fragment was quantified by ChemiDoc XRS system and Quantity One image analysis software (Bio-Rad Laboratories, Inc., Hercules, CA), and corrected by the intensity of β-actin transcripts level, which was expressed as relative intensity. The results are shown as an average from 8 subjects of each group (Fig. 1B).

Generation of Polyclonal Antihuman SOD3 Antiserum

Commercial antihuman SOD3 antiserum was not available at the time of the experiment; therefore, we used synthesized human SOD3 peptide as an antigen to generate polyclonal antiserum in New Zealand white rabbits according to previous reports. The sequence of SOD3 was analyzed by the Kyte-Doolittle method of calculating hydrophilicity, which indicated the region of amino acids 221 to 235, QAREHSERKKRRES, in the carboxyl-terminal end of SOD3 was strongly hydrophilic and contains several amino acids with a positive charge. This sequence probably confers the affinity of SOD3 for heparin and heparan sulfate.[14] The human SOD3 was produced under this basis with some modification. A peptide, containing residues of [(H2N-CQAREHSERKKRRRES)2-Lys]4-Lys2-Lys-βAla-OH, was constructed with 16 amino acids (QAREHSERKKRRRES plus cysteine) in the 5′-NH_2 terminal and with multiple antigenic peptides in 3′-COOH terminal. The synthesized peptide was analyzed by high-performance liquid chromatography and mass spectrum and then used as an antigen to generate polyclonal antiserum (antihSOD3) in New Zealand white rabbits. The titer of the rabbit antihSOD3 antibody was analyzed by dot blotting and enzyme-linked immunosorbent assay (ELISA).

ELISA of SOD Isoenzymes

The protein levels of SOD isozymes were analyzed by ELISA and Western blotting (WB). Ninety–six-well polyvinyl plates (Immulon II, Dynatech Labs, Chantilly, VA) were coated with 10 ng of total protein from extracts of nasal polyp tissues or control tissues in 10 0mol/L sodium carbonate, pH 9.6, and left overnight at 4°C. Plates were subsequently incubated with 3% bovine serum albumin for 30 minutes at room temperature to block nonspecific binding. Dilutions of primary antibodies (mouse antihuman SOD1 antibody [sc-17767, Santa Cruz Biotechnology, Santa Cruz, CA], goat antihuman SOD2 antibody [sc-18504, Santa Cruz], or rabbit antihuman SOD3 antiserum, ranging from 1:100 to 1:100,000,000) were added and incubated at room temperature for 1 hour. Dilutions (diluted 1:5,000) of corresponding horseradish peroxidase (HRP)-conjugated secondary antibodies (HRP-

TABLE II.
Sequences of Polymerase Chain Reaction Primers Specific to Superoxide Dismutase Isozymes and Beta-Actin.

Primer	Sequence	Annealing Temperature (°C)
SOD1	F: 5'-TAGCGAGTTATGGCGACGAA-3'R: 5'-CTTCATTTCCACCTTTGCCC-3'	57
SOD2	F: 5'-TTTTGGGGTATCTGGGCT-3'R: 5'-GCAGTACTCTATACCACTA-3'	57
SOD3	F: 5'-ATGCTGGCGCTACTGTGTT-3'R: 5'-GCTTCTTGCGCTCTGAGT-3'	57
β-actin	F: 5'-CCTTCCACCCCAGCCATGTA-3'R: 5'-CTTGCTCGAAGTCCAGGGCG-3'	57

F = forward; R = reverse.

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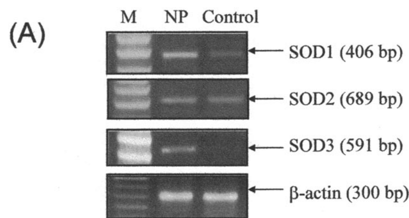


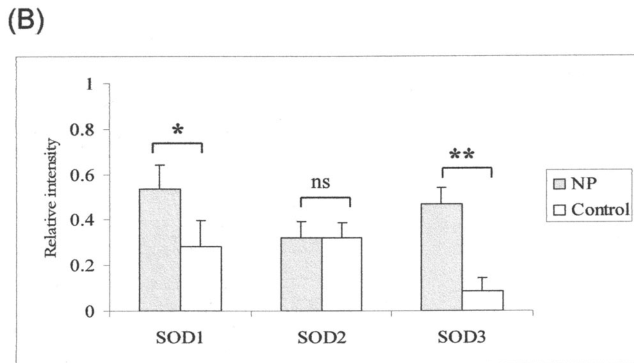


Fig. 1. (A) Reverse-transcription polymerase chain reaction analysis of superoxide dismutase isoenzymes mRNA in nasal polyps and control mucosa. M = marker; NP = nasal polyps. (B) Densitometric analysis of gel images. Intensity of each mRNA level per spot was quantified, corrected by the intensity of β-actin transcripts, and expressed as relative intensity; the results are shown as an average from eight subjects of each group. $^*P < .05$, $^{**}P < .01$, two-sample t test.

conjugated goat antimouse IgG [Leinco Technologies, Inc., St. Louis, MO], HRP-conjugated rat antigoat IgG [Leinco], or HRP-conjugated goat antirabbit IgG [Leinco]) were incubated for 1 hour each. Plates were washed extensively between additions throughout the entire experiment. The chromogen, ortho-phenylenediamine (Sigma) was added to visualize activity. Plates were read with an ELISA reader (MrX, Dynatech Lab.) at a wavelength of 490 nm. The assay was performed in duplicate, and the results were expressed as the mean ± SEM of triplicate extracts of nasal tissues from each subject of the two groups (Table III) (Fig. 2).

Western Blotting Analysis of SOD Isoenzymes

Fifty micrograms of total protein from extracts of nasal polyp tissues and control tissues were denatured and separated by sodium dodecylsulfate-polyacrylamide gel electrophoresis on 12% polyacrylamide gels. After transferring to a polyvinylidenfluorid membrane (PerkinElmer Life Science, Inc., Boston, MA), the blots were blocked with 5% nonfat skim milk in PBS and subsequently incubated with primary antibodies (diluted 1:5,000) (i.e., mouse antihuman SOD1 antibody [sc-17767, Santa Cruz],

TABLE III.
Expression Patterns of Superoxide Dismutase (SOD) Isoenzymes in Nasal Polyps (NP) and Control Mucosa Analyzed by Enzyme-Linked Immunosorbent Assay.

SOD Isozymes	NP	Control	*P* Value
SOD1	0.197 ± 0.023	0.165 ± 0.019	.048
SOD2	0.14 ± 0.021	0.128 ± 0.0254	.44
SOD3	0.14 ± 0.0097	0.059 ± 0.0085	.00045

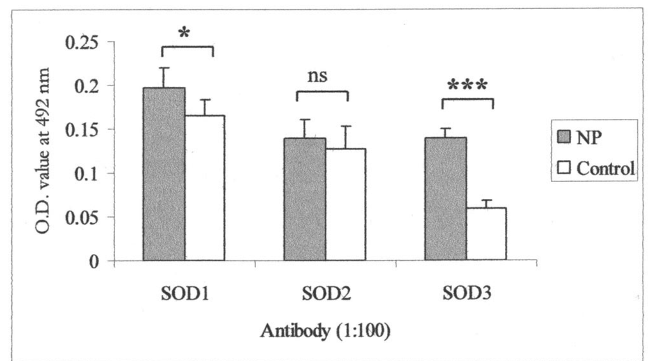
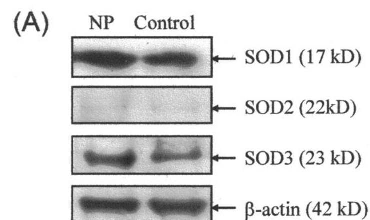


Fig. 2. Expressions of superoxide dismutase isoenzymes in nasal polyps and control mucosa analyzed by enzyme-linked immunosorbent assay. $^*P < .05$, $^{***}P < .001$, two-sample t test.

goat antihuman SOD2 antibody [sc-18504, Santa Cruz], or rabbit antihuman SOD3 antiserum) and treated with corresponding HRP-conjugated goat antimouse IgG (Leinco), HRP-conjugated rat antigoat IgG (Leinco), or HRP-conjugated goat antirabbit IgG (Leinco) secondary antibodies (diluted 1:5,000). After washing with PBS containing 0.5% Tween-20, peroxidase activity was visualized using the ECL Plus immunodetection system according to the manufacturer's instructions (NENTM Life Science, Boston, MA). The same membrane was reprobed with a monoclonal antibody directed against β-actin (diluted 1:5,000) (Sigma) and goat antimouse immunoglobulin secondary antibody (diluted 1:5,000) as a control for equal protein loading. The densitometry of the WB results was performed as that of RT-PCR (Fig 3).



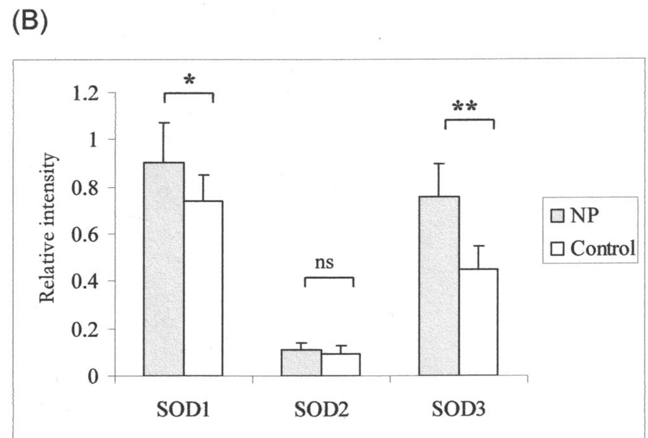


Fig. 3. (A) Western blotting analysis of superoxide dismutase isoenzymes in nasal polyps (NP) and control mucosa. (B) Densitometry of gel images. Intensity of each protein level per spot was quantified, corrected by the intensity of β-actin protein level, and expressed as relative intensity; results are shown as an average from eight subjects of each group. $^*P < .05$, $^{**}P < .01$, two-sample t test.

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Statistical Analysis

All values in the text and figures are expressed as mean (±SEM). Data were analyzed with two-sample *t* test by the SAS program for Windows, version 8.2 (Cary, NC). Differences in sex and age were examined by the Fisher's exact test. The level of statistical significance was defined as $P < .05$.

RESULTS

All of the eight NP patients were nonatopic, and NP in them manifested as severe or recurrent sinonasal polyposis clinically; the control subjects were also nonatopic. Demographic data of NP patients are listed in Table I. In the NP group, there were five men and three women, mean age 43.5 ± 12.8 years. In the control group (n = 8), there were four men and four women, mean age 39.3 ± 13.7 years.

The expression patterns of SOD isoenzymes evaluated by RT-PCR analysis indicated that the mean levels of SOD1 mRNA and, to a greater extent, SOD3 mRNA were higher in polyp tissues than in control tissues. However, there was no significant difference in the mean levels of SOD2 mRNA between the two groups (Fig. 1).

The expressions of SOD1, SOD2, and SOD3 analyzed by ELISA indicated that there were significant differences between the control and polyp groups in SOD3 and, to a lesser extent, in SOD1. However, there was no significant difference in the mean levels of SOD2 protein between the two groups (Table III) (Fig. 2).

The expressions of SOD1, SOD2, and SOD3 analyzed by WB also revealed that there were significant differences between the control and polyp groups in both SOD1 and SOD3, which paralleled the results obtained by RT-PCR. These findings were also consistent with those found by ELISA. There was no significant difference in the mean levels of SOD2 protein between the two groups (Fig. 3).

DISCUSSION

Our data derived from RT-PCR, ELISA, and WB studies indicated that the expression levels of SOD1 and, to a greater extent, SOD3 were increased in polyp tissues compared with control nasal mucosa. These results are consistent with previously reported data and support the hypothesis that oxidative stress exists in NP. However, the roles these SODs play in normal and diseased states are only slowly beginning to be understood.

The etiology of NP is an enigma; histologic studies appear to indicate that the pathophysiology is multifactorial. Various mediators such as adhesion molecules, cytokines, and inflammatory cells appear to be involved in the development and life cycle of NP.[2] There is growing evidence that oxidative stress plays a role in the pathophysiology of NP. Physiologically, FRs are kept in balance with the antioxidant defense system in the body, a condition called redox homeostasis. These ROS are normally controlled by the antioxidant defense mechanisms, including enzymatic antioxidants such as SOD, catalase and glutathione peroxidase, and nonenzymatic antioxidants, low-molecular mass compounds such as glutathione (GSH), α-tocopherol, β-carotene, retinol, and ascorbic acid. Oxidative stress ensues when there is an oxidant/antioxidant imbalance caused by an excess of ROS production or a depletion of antioxidants.[3] For example, MDA is a metabolite of FR-mediated lipid peroxidation, which can be used as an indicator of FR levels.[4,5] Dogru et al.[4] reported that MDA levels in NP from 19 patients were significantly higher than in mucosa from lateral lamella of the middle turbinates from 9 control subjects. Dagli et al.[5] investigated the role of FRs and antioxidants in NP from 31 patients compared with 19 control subjects. According to their results, in polyp tissue, the levels of oxidant (MDA) were increased, and the levels of antioxidant (GSH and α-tocopherol) were decreased compared with control tissues from inferior turbinates. Ruffoli et al.[6] also suggested that there exists progressive epithelium injury in nasal polyp tissues caused by peroxynitrite, a footprint maker of oxidative damage of protein.

NO is derived from the amino acid L-arginine and produced by the enzyme NOS. With its inhibitory effect on microorganisms and stimulating effect on ciliary motility, nasal NO keeps the sinuses sterile under normal conditions by aiding clearance of organisms and toxins.[10,11] Colantonio et al.[11] found that NO levels correlated directly with the extent of polyposis and that successful treatment, with reduction in polyp volume, was associated with a rise in NO levels. They proposed that the decrease in NO levels was possibly related to blockage of the ostiomeatal complex and failure of NO to reach the nasal airway, which is generated constitutively in the sinuses, and is the major contribution of nasal NO.

However, there is at least one more reason which might account for the decrease in NO levels seen in NP. SOD3 might play a role as both an antioxidant and a regulator of signaling. In inflammatory diseases, including asthma and NP, inflammatory cells, such as eosinophils, neutrophils, and macrophages, not only produce ROS but also make NO by up-regulating iNOS.[8] It is well known that increased ROS reacts extremely with NO. For instance, NO rapidly reacts with superoxide to form peroxynitrite, hydroxyl radicals to form nitrite, and peroxyl radicals to form alky-peroxynitrite. These reactions might decrease the concentration of NO, thereby diminishing its bioavailability.[7,8] Pasto et al.[7] evaluated the relationship between NO concentrations and production of superoxide in nasal polyps from 24 patients. They found phagocytic-derived superoxide appears to contribute to the reduction of sinus NO concentration, further altering this natural local defense. Therefore, they concluded that these events could participate in chronic inflammation and contribute to the pathophysiology of NP. Also, the presence of oxidase and ROS scavenging enzymes near areas of NO signaling (e.g., airway smooth muscle) suggests that modulation of ROS concentrations by antioxidant enzymes (e.g., EC-SOD) might be one method of regulating NO signaling.[8]

In this study, the most evident difference observed in the expression of SODs between NP and control groups was SOD3. SOD3 (EC-SOD) is primarily an EC-SOD enzyme and is quite distinct from intracellular SOD1 and SOD2. For example, the levels of EC-SOD in the aortic wall are known to vary widely among species. The level of EC-SOD in human aortic wall was shown to be approximately 70 times higher than that in rat aortic wall on average; however, there were only moderate differences in

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the amounts of CuZn-SOD and Mn-SOD.[15] Again, in humans, SOD3 mRNA is abundant in airway epithelium and vascular endothelium and is expressed at levels 4 times that seen in the heart and 15 times that seen in the liver.[8] This wide variation in EC-SOD content suggests that the susceptibility to pathologies induced by superoxide radicals in tissues should vary widely among species as well as among organs in one species. Moreover, the expression of SOD3 is highly restricted to the specific cell types and tissues, where its activity can exceed that of SOD1 and SOD2.[9] Furthermore, the predominant expression of SOD3 around airways and airway smooth muscle suggests that it might play a role in inflammatory airway diseases.[8]

Our data also suggested that there were no differences in the expression of SOD2 between NP and control groups. In fact, the promoter regions of SOD2 in all four species, human, rat, mouse, and bovine, share common features. No upstream TATA or CAAT box elements have been identified; however, guanine phosphate cytosine—rich (Gp(—rich) regions are present in all four species. Such features are typical of "housekeeping" genes.[9]

To date, most of our knowledge about inflammation-induced oxidative stress of the respiratory tract comes from studies of physiology and pathology of the lower airway. Steroid therapy attenuates hydrogen peroxide, nitrotyrosine, and ethane formation; augmentation of existing antioxidant defenses with catalytic antioxidants (e.g., intraperitoneal SOD in animal models) reduced airway hyperresponsiveness.[8] These results suggest that oxidative stress is an important factor in the pathogenesis of airway inflammation and that both antiinflammatory and antioxidant agents can potentially be useful adjunct therapies. In contrast with abundant results gathered from lower airway diseases, the role SOD isoforms play in the pathogenesis of NP is unclear. However, the concept "one airway, one disease" warrants the need to investigate NP, a common comorbidity sharing similar pathophysiology with asthma.[2,8]

CONCLUSION

Our data indicated that the expressions of SOD3 and, to a lesser extent, SOD1 were higher in polyp tissues than in control mucosa. SOD isoforms, which play a role as both an antioxidant and a regulator of signaling, might also play a role in the pathogenesis of NP. This may reflect the complexity of the redox reactions in a biological system and even in the disease process. However, the relationship among oxidative stress, NO activity, NOSs, and SODs as well as the therapeutic implications in NP remain to be clarified.

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