Production of 3-Nitrotyrosine in the Nasal Polyps and its Possible Role in the Pathogenesis and Recurrence

Thesis

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List of Contents

Subject	*Page No.*
List of Abbreviations	**i**
List of Tables	**iii**
List of Figures	**v**
Introduction	**1**
Aim of the Work	**4**
Review of Literature	
Definition and Overview	5
Epidemiology & Classification	11
Etiopathogenesis	16
Diagnosis	26
Nitric oxide	29
Materials and Methods	**41**
Results	**47**
Discussion	**72**
Conclusions	**81**
Summary	**82**
References	**86**
Arabic Summary	**–**

List of Abbreviations

Abbr.	Full-term
ASA triad	: Samter's triad
CC	: Ciliated cells
CF	: Cystic fibrosis
CFTR	: Cystic fibrosis trans-membrane regulator
CRS	: Chronic rhinosinusitis
CT	: Tomography scans
ECP	: Eosinophilic cationic protein
eNOS	: Endothelial nitric oxide synthase
EPO	: Eosinophil peroxidase
FORs	: Free oxygen radicals
FR	: Free radicals
GC	: Goblet cells
GM-CSF	: Granulocyte-macrophage-colony stimulating factor
H&E	: Hematoxylin-eosin
iNOS	: Inducible nitric oxide synthase
3-NT	: 3-Nitrotyrosine
MDA	: Malondialehyde
MMP-9	: Matrix metalloproteinase-9
MRI	: Magnetic resonance image
nNOS	: Neuronal nitric oxide synthase
NO	: Nitric oxide
NOS	: Nitric oxide synthase

List of Abbreviations

Abbr.	Full-term

NP : Nasal polyps

NRE : Nasal respiratory epithelium

O_2- : Superoxide anion

ONOO : Peroxynitrite

PPS : Phosphate-buffered solution

RANTES : Regulated on Activation Normal T Expressed and Secreted

RM : Respiratory mucosa

ROC : Receiver-operating characteristic

ROS : Reactive oxygen species

SD : Standard deviation

SEA : Staphylococcus enterotoxins A

SEB : Staphylococcus enterotoxins B

SOD : Superoxide dismutase

TNF : Tumor necrosis factor

TSST-1 : Toxic shock syndrome toxin-1

List of Tables

Table No.	Title	Page No.
Table (1):	Characteristics of cases and controls	48
Table (2):	Characteristics of patients with newly excised or recurrent nasal polypi	49
Table (3):	Number of previous surgeries in the recurrent nasal polypi group.	50
Table (4):	Characteristics of patients with recurrent NP who underwent one previous surgery and those who underwent two or more previous surgeries	51
Table (5):	Eosinophil count and epithelial damage score in cases and controls	54
Table (6):	Eosinophil count and epithelial damage score in patients with newly excised or recurrent nasal polypi	57
Table (7):	Correlation between the eosinophilic count and the frequency of recurrence in the recurrent NP group	61
Table (8):	Eosinophil count and epithelial damage score in patients with recurrent NP who underwent one previous surgery and those who underwent two or more previous surgeries	62

List of Tables *(Cont.)*

Table No.	Title	Page No.
Table (9):	Receiver-operating characteristic (ROC) curve analysis for the value of the eosinophil count for differentiation between cases with NP and control.	68
Table (10):	Receiver-operating characteristic (ROC) curve analysis for the value of the eosinophil count for differentiation between cases with newly excised or recurrent nasal polyls	69
Table (11):	Multivariable linear regression analysis for the effect of bronchial asthma and aspirin allergy on the eosinophil adjusted for age, gender and recurrence of polyps	70
Table (12):	Multivariable logistic regression analysis for the effect of bronchial asthma and aspirin allergy on the severity of epithelial damage as adjusted for age, gender and recurrence of polyps	71

List of Figures

Figure No.	Title	Page No.
Figure (1):	Normal nasal mucosa showing respiratory epithelium with columnar ciliated cells and goblet cells (Hx & E × 400)	52
Figure (2):	Nasal polypi with moderate epithelial damage, the ciliated and goblet cells are present; several irregular spaces are seen; eosinophils are present in the subepithelial tissue (Hx & E × 400)	53
Figure (3):	Nasal polypi with severe epithelial damage, the ciliated and goblet cells are absent; the connective tissue is edematous and highly infiltrated by eosinophils (Hx & E × 400)	53
Figure (4):	Eosinophilic infiltrate in nasal polypi (Hx & E × 400)	55
Figure (5):	Epithelial damage score in patients with newly excised or recurrent nasal polyps.	58
Figure (6):	Mean eosinophil count in patients with newly excised or recurrent nasal polyps.	60
Figure (7):	Mean eosinophil count in patients with recurrent nasal polyps who underwent one previous surgery and those who underwent two or more previous surgeries.	63

List of Figures *(Cont.)*

Figure No.	Title	Page No.
Figure (8):	Epithelial damage score in patients with recurrent nasal polyps who underwent one previous surgery and those who underwent two or more previous surgeries.	64
Figure (9):	Nasal mucosa from control group, 3-Nitrotyrosine staining is absent (Ni, 400)	65
Figure (10):	Positive staining of eosinophils with 3-Nitrotyrosine (Ni, 400)	66
Figure (11):	Nasal mucosa with moderate epithelial damage, the 3-Nitrotyrosine is found as brown precipitate in the epithelial cells and eosinophils (Ni, 200)	66
Figure (12):	Nasal mucosa with severe epithelial damage, the 3-Nitrotyrosine is found as brown precipitate in the epithelial cells and eosinophils (Ni, 400)	67

Introduction

Nasal polyps (NP) are benign proliferations of the nasal mucosa characterized by chronic inflammatory status. (Typically originating from the ethmoid epithelium) ***(Karlidağ et al., 2005).*** Histologic examinations have shown that NP consist of an epithelium covering a lamina propria with large infiltrations of inflammatory cells ***(Hellquist, 1996; Larsen et al., 1998; Pawankar, 2003).***

The predominant cell found in the inflammatory infiltrate is the eosinophil. The covering epithelium shows various degrees of modification from normal respiratory epithelium ***(Bernstein et al., 19997; Kramer and Rasp, 1999; Mygind et al., 2000).***

They are the most common mass lesion found in the nose and tend to recur despite medical and surgical therapy. The pathophysiologic mechanism leading to formation of NP have not been clearly understood ***(Larsen et al., 1998; Kramer and Rasp, 1999; Mygind et al., 2000; Pawankar, 2003).***

Theories have been proposed that the origin of NP is multifactorial and that NP are a consequence of systemic diseases or local inflammatory processes. Traditionally allergy has been considered a major cause of the nasal polyposis, but several evidences do not agree with this opinion ***(Larsen, 1998; Bernstein et al., 1997; Bateman et al., 2003).***

Indeed, NP do not occur with increased frequency in atopic individuals, and patients with NP do not have a positive allergy skin test more often than control subjects ***(Mygind et al., 2000; Bateman et al., 2003).***

Several lines of evidence have indicated that the diffusible free radical nitric oxide (NO) plays a crucial role in the pathophysiology of airway disease and in the control of the airway inflammation ***(Gaston et al., 1994).***

NO is produced from L- arginine by a group of three distinct isoforms of nitric oxide synthase (NOS). Two isoforms are continuously present and termed constitutive NOS. The third isoform, named inducible NOS (iNOS) is not generally expressed in resting cells, but it may be induced by cytokines and microbial products to produce large quantities of NO for a long period of time ***(Förstermann et al., 1995).***

In the airway inflammatory disease, an excessive formation of NO caused by iNOS expression may cause tissue damage. This mainly originates from production of highly reaction Nitrogen species by way of interactions of NO with reactive oxygen species (ROS) ***(Flak and Goldman, 1996; van der Vliet et al., 1999; Robbins et al., 2000).***

Reaction of NO with superoxide anion generates the potent oxidant peroxynitrite, which may cause severe tissue

injury. In addition, peroxynitrite nitrates tyrosine residues of proteins leading to formation of the stable product 3–Nitrotyrosine (3NT), which is considered an indicator of oxidative damage in many diseases ***(Ischiropoulos, 1998)***, including those of the airway ***(van der Vliet et al., 1999; Ichinose et al., 2000; Robbins et al., 2000; van der Vliet, 2000).***

Presence of 3NT has been observed in the respiratory mucosa of asthmatic patient and in the nasal respiratory mucosa of patients affected by allergic rhinitis ***(Sato et al., 1998; Kang et al., 2000).***

Studies documented the expression of iNOS in the epithelium and the inflammatory cells of the NP. But studies concerning presence of 3NT in the NP are few and did not focus on its role in recurrence of NP.

Aim of the Work

This work aims at:

Comparing 3- NT production in nasal polyps patients and non-nasal polyp subjects in order to study its possible role in the pathogenesis of NP formation and recurrence, as an indicator of oxidative damage in this disease.