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REVIEW

The Dual Role of Nitric Oxide in Allergic Rhinitis: From the NO/cGMP Signaling Pathway to Possible New Therapeutic Targets for Organelle Damage

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Abstract: Allergic rhinitis (AR) is a chronic, non-infectious condition mediated by IgE that primarily affects the nasal mucosa. Recent studies have indicated a relationship between nitric oxide (NO) and the pathogenesis of allergic rhinitis. This review integrates the NO/cGMP pathway with mitochondrial, endoplasmic reticulum, and lysosomal pathways, as well as related translational targets, aiming to systematically dissect the associations between these pathways and their roles in AR. By synthesizing literature from the PubMed database (1994–2024), we conducted an in-depth analysis of the specific mechanisms by which homeostatic NO and pathological NO contribute to the pathogenesis of AR. Additionally, we investigate the impact of the NO derivative peroxynitrite on mitochondrial, endoplasmic reticulum, and lysosomal organelles. Based on these findings, we further explore potential treatment modalities for AR.

Keywords: nitric oxide, NO/cGMP, allergic rhinitis, peroxynitrite, cellular components

Introduction

Allergic rhinitis (AR), classified by course as intermittent (seasonal) or persistent (perennial), is characterized by typical symptoms including sneezing, ocular-nasal-pharyngeal itching, nasal congestion, and rhinorrhea.[1] As a global health concern, AR affects approximately 10–40% of the world's population, with prevalence continuing to rise in developed nations.[2] Studies indicate that seasonal allergens (eg, grasses, ragweed) and perennial allergens (eg, dust mites, pet dander, cockroach feces) often yield positive IgE test results.[1] Additionally, the incidence of AR is closely associated with nasal nitric oxide (NO) levels, which provides a direction for elucidating the mechanisms of nasal allergic inflammation.[3]

AR impacts health across multiple dimensions: it can cause fatigue, emotional disturbances, cognitive impairment, and even secondary depression and anxiety.[4] The economic burden is also substantial, with direct and indirect costs from AR exceeding $50 billion annually in China, the United States, and the EU region.[5–7]

Current AR management primarily involves environmental control, pharmacologic intervention, and allergen immunotherapy,[1] yet diagnostic and therapeutic challenges persist: nearly 70% of patients rely on over-the-counter medications for self-management, and only 44.3% receive professional diagnosis.[8] Complete avoidance of allergen exposure remains difficult, and long-term medication use fails to achieve cure. Therefore, in-depth exploration of AR pathophysiology is crucial for optimizing clinical management and developing novel therapeutic strategies.

In ancient times, NO converted from atmospheric nitrogen was utilized by plants and bacteria, demonstrating its key role in biology.[9] In 1980, a pharmacologist identified that the substance released by endothelium, which acetylcholine relies on for vasodilation, is NO.[10] Present in mammalian cells, it involves multiple system functions, metabolism and immunity, and is crucial for signal transduction.[11] In the pathogenesis of AR, the NO/cyclic guanosine monophosphate

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(cGMP) signaling pathway can enhance the allergic response of the nasal mucosa in AR patients, exacerbating symptoms such as nasal congestion, a runny nose, and itching.[12] At the same time, NO was involved in the nitrification stress response, which can result in organelle damage and cell death, subsequently leading to damage of the nasal mucosa and exacerbating nasal inflammation.[13,14] Compared with the research focus of previous studies on NO in AR, this paper mainly focuses on the specific mechanisms of action of homeostatic NO and pathological NO in AR, as well as the effects of NO and its derivatives on organelles.

A Comprehensive Review of AR

Epidemiology

AR currently impacts around 10%-40% of people worldwide, and its prevalence is steadily increasing in more developed nations.[2] In the United States, the affected population ranges from 10% to 20%, while in Europe, it is between 23% and 30%.[15,16] In non-Western populations of the Southern Hemisphere, the prevalence of AR exhibits significant disparities, with substantial fluctuations not only between nations but also within regions, ranging approximately from 2.9% to 54.1%.[17] Due to China's vast territory and large population base, national-level specific statistics are currently lacking. A recent extensive investigation across 18 significant cities in China has indicated a general increase in the self-reported prevalence of AR among the adult population in China for the years 2005 to 2011.[18] The treatment of AR in these countries or regions incurs significant costs. Each year, AR costs the US healthcare system an estimated $4.9 billion in direct costs. This figure nearly doubles when indirect costs—such as lost work time, missed diagnoses, and over-prescribing—are taken into account.[5] In countries within the European Union, it is estimated that annual economic losses range from 30 billion to 50 billion euros.[6] In China, the estimated total cost of AR is approximately $17.49 billion, which includes only the costs associated with medication.[7] Consequently, from a global perspective, the economic losses associated with AR are substantial.

Etiology

Mast cells serve as core effector cells in allergic reactions, with their functional activation primarily achieved through degranulation - a process triggering the release of numerous allergic mediators. Mast cell degranulation is predominantly initiated via IgE-dependent mechanisms, where allergen binding to IgE antibodies induces cross-linking activation of high-affinity receptors (FcεRI).[19] A minor fraction involves IgE-independent degranulation directly mediated by stimuli such as complement fragments, neuropeptides, or cytokines.[20] The etiology of AR primarily involves immune regulation, neuro-immune regulation, and microbiome regulation (Figure 1). Among them, immunomodulation belongs to IgE-dependent degranulation, while neuro-immune regulation and microbiota regulation fall under IgE-independent degranulation.

Immunomodulation

In the process of immunomodulation, IgE-dependent mast cell degranulation plays a key role. When nasal mucosa encounters allergens, dendritic cells (DCs) capture and process antigens. Activated DCs migrate to local mucosa or lymph nodes, presenting allergenic peptides to naive T cells and inducing their differentiation into Th2 cells. Driven by IL-4, Th2 cells secrete cytokines such as IL-13, which collaborate with costimulatory molecules to promote B cell class switching and production of IgE antibodies. IgE attaches to FcεRI found on the surfaces of mast cells and basophils through the bloodstream, thus sensitizing these cells.[21]

IgE-mediated mast cell degranulation is the core pathological process of hypersensitivity reactions in AR. Its signal transduction mainly relies on two key pathways, with the specific mechanism of the Lyn-dependent activation pathway as follows: When IgE binds to FcεRI (the high-affinity IgE receptor) on the surface of mast cells, Lyn—a kinase belonging to the Src family—is activated. This activated Lyn then initiates the PLC-γ signaling pathway, which fulfills two key functions: first, it promotes the release of Ca^{2+} from intracellular calcium stores; second, it indirectly triggers the activation of protein kinase C (PKC). As a critical regulator of degranulation, PKC ultimately facilitates the rapid release of preformed inflammatory mediators, such as histamine and proteases.[22]

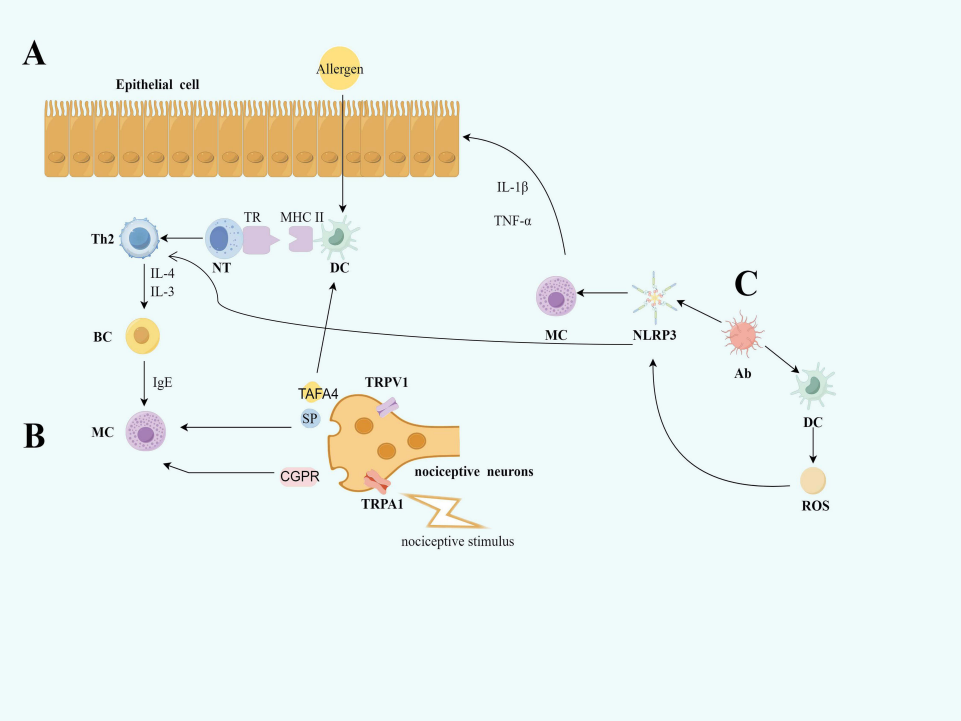

Figure 1 There are three main causes of AR. (**A**) The allergen irritates the nasal mucosa and is captured by DCs. This process leads to the activation of DCs, which present allergy-derived peptides to naive T cells through major histocompatibility complex class II (MHC II). Consequently, the T cells are prompted to differentiate into Th2 cells, which produce IL-4 and IL-13 to stimulate B cells and induce the production of IgE to sensitize mast cells. (**B**) External stimuli interact with neuronal membranes and can activate harmful neurons by targeting TRPV1, TRPA1, and other receptors. Nociceptive neurons release neuropeptides, such as SP, CGRP and TAFA4, which induce mast cells to become sensitized. (**C**) In the case of Acinetobacter baumannii, it activates the NOD-like receptor NLRP3, which promotes the release of IL-1β and TNF-α by macrophages, thereby triggering AR. Additionally, Acinetobacter baumannii induces dendritic cells to produce reactive oxygen species, which activate NLRP3 and promote cell differentiation into pro-inflammatory Th2 cells, thereby triggering an immune response characteristic of AR.

Abbreviations: DC, Dendritic Cell; Th2, T helper 2 cell; SP, Substance P; NT, Naive T cell; BC, B Lymphocyte; MC, Macrophage; TAFA4, thymus activation regulated chemokine 4; CGPR, Calcitonin Gene-Related Peptide; TRPV1, Transient Receptor Potential Vanilloid 1; TRPA1, Transient Receptor Potential Cation Channel Subfamily A Member 1; Ab, Acinetobacter baumannii; NLRP3, Nucleotide-binding Oligomerization Domain-Like Receptor Pyrin Domain Containing 3; ROS, Reactive Oxygen Species.

The Fyn-dependent activation pathway is similar to the Lyn activation mechanism in that both rely on receptor signal transduction following FcεRI aggregation, and its process consists of two core stages: signal transduction and molecular recruitment (after FcεRI aggregates due to IgE binding, activated Fyn mediates the activation of Gab2 through phosphorylation, and the activated Gab2 then specifically binds to the p85 regulatory subunit of PI3K) and key product generation with calcium signal initiation (the bound PI3K catalyzes the production of PIP3, which regulates the activity of calcium channels on the cell membrane to promote Ca^{2+} influx and release, thereby providing the necessary calcium signals for mast cell degranulation).[23] These mechanisms induce immediate hypersensitivity reactions, such as increased nasal mucosal vascular permeability leading to nasal congestion and histamine-stimulated nerve endings causing nasal itching.

Neuro-Immune Regulation

Neuro-immune regulation refers to the complex network of interactions between nociceptive neurons and immune cells. Nociceptive neurons are specialized peripheral sensory neurons that encode painful stimuli.[24] They can detect potentially harmful stimuli encountered by the body, such as mechanical injury, high temperatures, and chemical irritation. These neurons then convert such stimuli into neural signals, which are transmitted to the brain via the nervous system. Ultimately, this process enables the body to generate the subjective sensation of "pain" and thereby triggers protective responses.[25,26] The nociceptive neurons in the nasal mucosa primarily include the maxillary nerve of the trigeminal nerve and the optic nerve. When various physical or chemical stimuli activate the Transient Receptor Potential Vanilloid 1 and the Transient Receptor Potential Cation Channel Subfamily A Member 1 and other receptors, nociceptive neurons release

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neuropeptides such as Substance P and Calcitonin Gene-Related Peptide. This process can trigger an immune response in AR, prompting the activation of immune cells such as mast cells and basophils. These activated immune cells then further release inflammatory mediators including histamine and cytokines. Such inflammatory mediators can significantly enhance the excitability of nociceptive neurons, ultimately forming a positive feedback regulatory mechanism that continuously amplifies the stimulatory effect.[26]

Microbiome Regulation

Microbiome regulation refers to the human microbiome's ability to maintain a balance of immunity that protects individuals from allergies and other inflammatory conditions.[27] Studies have found that differences in the nasal microbiome are potential mechanisms underlying the pathogenesis of diseases.[28] Che et al examined the characteristics of the nasal microbiome in patients who have AR compared to those with non-allergic rhinitis (NAR). The researchers observed that the relative abundance of Vibrio vulnificus and Acinetobacter baumannii was notably greater in the AR group.[29] Acinetobacter baumanni can harbor various virulence factors, including pore-forming toxins and reactive oxygen species (ROS), which activate the NLRP3 inflammasome, thereby promoting the immune response typically associated with asthma and AR.[30] Additionally, Vibrio vulnificus can induce the production of cytokines such as IL-1β, IL-6, and TNF-α. This activation of neutrophils, monocytes, macrophages, and other immune cells triggers inflammation.[31] Vibrio vulnificus can also exert anti-inflammatory effects by inhibiting the proliferation of Kupffer cells, which is consistent with the pathogenesis of AR.[32]

Clinical Manifestations and Treatment of AR

AR is a nasal symptomatic condition characterized by an IgE-mediated allergic response to environmental allergens, leading to an infection-like inflammatory reaction.[7] Allergens can be categorized into outdoor and indoor types based on environmental origin. Typical allergens found outdoors encompass pollen and molds, while those present indoors consist of dust mites, molds, cockroaches, and pet dander.[33] Notably, allergen profiles are not absolute but are inherently linked to regional environments: for instance, Artemisia species represent the primary allergen in western China, while Photinia davidiana (redleaf photinia) is the most prevalent allergen in Guangzhou.[34] The symptoms encompass nasal blockage, a runny nose (rhinorrhea), postnasal drainage, and frequent, abrupt sneezing. Additionally, patients might encounter further signs including a cough, nasal itchiness, conjunctivitis, and congestion in the upper respiratory tract.[5] As per the guidelines from the Allergic Rhinitis and its Impact on Asthma (ARIA), AR is divided into two types: intermittent and persistent, depending on the length of the symptoms experienced. Furthermore, it is categorized as mild or moderate-severe based on the intensity of symptoms.[6] Symptoms that are persistent happen more than four times each week and continue for over four weeks, whereas intermittent symptoms arise less frequently, occurring fewer than four times weekly and lasting for fewer than four weeks.[35]

No single treatment is universally effective in managing AR. Common treatment options include environmental control, pharmacotherapy, and allergen immunotherapy.[1] The primary focus of first-line treatment is to eliminate environmental triggers of symptoms, such as dust mites, pet dander, and mold spores. According to the guidelines for treating AR, medication is recommended for patients over 12 years of age, with various treatment options available.[36] For patients with intermittent AR, first-line treatment primarily involves second-generation oral antihistamines and nasal antihistamines. Clinically, second-generation antihistamines (eg, cetirizine, loratadine, fexofenadine) are often combined with intranasal corticosteroids (eg, mometasone furoate, budesonide) for treating allergic rhinitis. Compared with first-generation antihistamines (eg, diphenhydramine, promethazine), second-generation agents offer better safety profiles with fewer sedative and hypnotic adverse effects.[37] For patients experiencing various symptoms of persistent allergic rhinitis, the first-line treatments differ. For individuals with mild symptoms, nasal corticosteroids are typically recommended. In cases of moderate to severe symptoms, nasal corticosteroids, nasal antihistamines, or a combination of both may be utilized (Figure 2).[36]

There are several options for allergen immunotherapy, with subcutaneous and sublingual immunotherapy being the most effective. Both have been approved by the US Food and Drug Administration.[38] While both methods are well-respected, subcutaneous immunotherapy has a probability of triggering systemic adverse reactions at a rate of 1 in 1000,

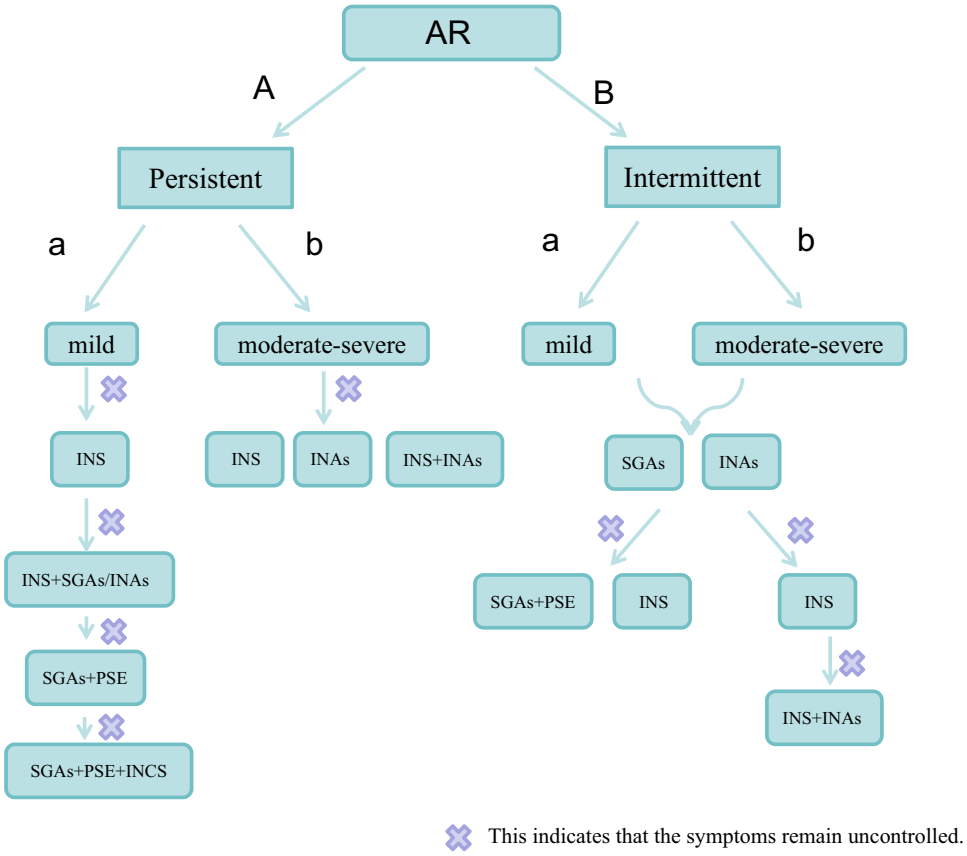

Figure 2 Drug treatment plans for patients aged 12 and older with allergic rhinitis. For patients with various types of allergic rhinitis, if first-line medications are ineffective, it is advisable to consider second-line treatments, and so forth. (**A**) Symptoms occur more than four times per week over a period of more than four weeks. (**B**) Symptoms occur fewer than four times per week over a duration of less than four weeks. a: The patient's symptoms do not interfere with their daily life. b: The patient's symptoms do interfere with their daily life.

Abbreviations: INS, Intranasal corticosteroids; INAs, Intranasal antihistamines; SGAs, Second - generation antihistamines; PSE, Pseudoephedrine; INCS, Intranasal Cromolyn Sodium.

with a life-threatening risk occurring at a rate of 1 in 160,000.[39] Additionally, approximately 50% of patients receiving sublingual immunotherapy report experiencing itching in the mouth and palate, as well as heightened anxiety.[40]

A Comprehensive Review of NO

The Pathway That Produces NO in the Body

NO is a colorless gas with complex chemical properties.[41] There are two primary methods for producing NO in the human body: one involves the decomposition of inorganic substances within the body or photolytic reactions occurring on the skin's surface. The other method is through the enzymatic catalysis of nitric oxide synthase (NOS).[42,43] Three primary varieties of nitric oxide synthase (NOS) include neuronal nitric oxide synthase (nNOS), inducible nitric oxide synthase (iNOS), and endothelial nitric oxide synthase (eNOS).[11] These enzymes are distributed in different locations: nNOS is primarily found in peripheral and central nervous tissues, eNOS is mainly located in vascular endothelial cells, and iNOS is commonly present in immune cells. nNOS and eNOS produce low levels of NO in a pulsatile manner, while iNOS continuously generates high-dose NO at the micromolar level under inflammatory stimulation.[44] Low-dose NO can activate the cGMP/PKG signaling pathway, whereas high-dose NO primarily induces nitrosative stress. During inflammation, massive expression of iNOS significantly elevates NO levels.[45–47] Excessive accumulation of intracellular NO leads to a reaction with superoxide radicals, resulting in the formation of reactive nitrogen species (RNS) that consequently damage cellular DNA.[48] Moreover, existing clinical and experimental studies have confirmed a clear association between NOS expression and AR (Table 1).

Table 1 Comparison of NOS Expression in Clinical and Experimental Data Between AR Patients or Animals

Experimental Subjects	Type of Study	Types of NOS Isoenzymes	Location of NOS	Results
AR patients	Clinical	iNOS	Inferior turbinate (epithelium, endothelium, glandular tissue)	Immunohistochemical detection of iNOS expression showed that the expression intensity of iNOS in the glandular tissue of the allergic group was higher than that in patients with non - allergic rhinitis.[49]
Seasonal AR patients	Clinical	eNOS/iNOS	Inferior turbinate	The immunohistochemical expression of eNOS showed no significant difference between the seasonal AR group and the nAR group (P = 0.12). However, the expression of iNOS was greater in the seasonal AR group (P = 0.04).[50]
AR patients	Clinical	iNOS	Serum	AR patients who underwent and completed 1-year subcutaneous immunotherapy were categorized into effective and ineffective groups. Serum iNOS levels were significantly elevated in AR patients compared to healthy controls. Notably, the responsive group exhibited markedly higher serum iNOS levels than the non-responsive group.[51]
AR patients allergic to house dust mites	Clinical	eNOS/iNOS	Inferior turbinate (epithelial cells)	When utilizing a laser confocal microscope to examine iNOS and eNOS, it was found that the expression level of iNOS in the epithelial cells of the AR group was notably greater than that in the control group. However, there was no significant difference in eNOS expression between the AR group and the normal group.[52]
AR patients	Clinical	nNOS	Inferior turbinate and middle turbinate mucosa	The immunohistochemical method was employed to identify nNOS. The results showed that the immune staining in glandular sections beneath the mucosa of individuals with allergic rhinitis was more intense compared to those with idiopathic rhinitis and those without nasal congestion.[53]
AR guinea pigs*	Animal	eNOS/iNOS	Nasal mucosa	The guinea pigs were allocated into an AR group, a treatment group, and a normal control group. Immunostaining results showed distinct eNOS expression in the nasal mucosa of both the AR and treatment groups, while eNOS expression was markedly lower in the normal control group. By contrast, no significant intergroup differences were found in iNOS expression.[54]

Notes: *Compared with human patients with allergic rhinitis, the pathogenic isoform in the guinea - pig model of allergic rhinitis is eNOS rather than iNOS. Therefore, the results in guinea - pigs are inconsistent with those in human patients.[4]

Abbreviations: AR, Allergic rhinitis; NOS, nitric oxide synthase; nNOS, neuronal nitric oxide synthase; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase.

The Physiological Role of NO

NO plays a crucial role in various systems within the human body. Research has shown that NO is capable of modulating blood flow in tissues through the dilation of vascular smooth muscle, the suppression of cell proliferation, and the promotion of apoptosis.[55] In the nasal mucosa, NO promotes the ciliary beat frequency of epithelial cells and regulates ciliary movement to enhance antibacterial ability.[55–57] In addition, NO is significant in motor regulation, energy balance, and learning through the NO/cGMP signaling pathway.[57] In this signaling pathway, NO can freely diffuse to adjacent cells, activate and bind to the nitric oxide receptor (soluble guanylate cyclase), catalyze guanosine triphosphate (GTP) to produce the second messenger cGMP, and subsequently activate the downstream effector protein cyclic guanylate-dependent protein kinase G (PKG) to perform various physiological functions.[58] Its specific manifestations are as follows: PKG reduces intracellular calcium ion concentration by phosphorylating myosin light chain phosphatase and calcium-activated potassium channels, thereby promoting vascular relaxation and regulating blood pressure;[59] in addition, PKG alleviates bronchial smooth muscle contraction by activating potassium channels and inhibiting calcium

signaling pathways, a mechanism that contributes to the regulation of respiratory diseases such as asthma,[60] among others.

The Relationship Between Nitrification Stress and NO

Nitrification stress refers to the biochemical reaction between NO and its derived RNS, as well as reactive oxygen species. This process is characterized by the excessive production of peroxynitrite ($ONOO^-$), which leads to the oxidation of proteins, lipids, and DNA, ultimately triggering cell death.[61,62] $ONOO^-$ targets various organelles, such as the mitochondria, endoplasmic reticulum, and Golgi apparatus, to induce cell death.[61] For example, $ONOO^-$ affects the mitochondrial respiratory chain, including cytochrome c oxidase and ATP synthase, thereby promoting mitochondrial apoptosis.[63] Additionally, it accumulates in the endoplasmic reticulum, damaging its physiological function.[64] Furthermore, $ONOO^-$ can also mediate oxidative damage to Golgi apparatus-related proteins, leading to the breakdown of the Golgi apparatus in ischemic animal models.[65]

Relationship Between NO and AR

NO and its related derivatives, along with signaling pathways, constitute a complex regulatory network in the pathogenesis of AR. From the direct effects of abnormal NO concentration on nasal mucosal cells, to the allergic reactions triggered by cascade activation of the NO/cGMP signaling pathway, and to oxidative stress damage mediated by toxic derivatives such as $ONOO^-$, these links participate in the occurrence and development of AR through different mechanisms (Table 2). The following systematically analyzes the specific action mechanisms of NO-related substances and signaling pathways in AR focusing on three core directions.

NO and AR

Changes in NO in allergic diseases have been identified in studies involving patients with asthma. It has been proposed that the respiratory inflammatory response is positively correlated with fractional exhaled nitric oxide levels.[3] Gori et al's study demonstrated that in children with AR, after treatment with Quertal (a nutraceutical supplement derived from *Perilla frutescens*) in combination with antihistamines, the children's nasal nitric oxide (nNO) levels decreased by 30% compared to the baseline.[76] However, Keon et al found that fractional exhaled nitric oxide concentrations were significantly higher in patients with persistent AR, while nNO concentrations were significantly lower in the intermittent group,[77] which may be related to the velocity of the nNO testing instrument, the patients' age, and the timing of

Table 2 Summary Table of the Mechanisms of Action of NO and Its Derivatives/Signaling Pathways in AR

No and Derivatives	Mechanism of Action	Specific Impact Mechanism	Reference
NO	Regulation of nasal mucosa related cells	• Stimulate goblet cells to secrete mucin • Inhibit mitotic activity of basal cells • Regulation of ciliated cell activity	[66–68]
$ONOO^-$	• Oxidative stress • InjuryAllergen immunogenicity is enhanced • Disruption of organelle function	• Activation of the GATA-3/T-bet pathway and nitrosogenic stress can induce nasal symptoms in AR mice • Nitrogenated modification of birch pollen Bet v 1, dust mite Der p 2, enhanced IgE binding • It damages mitochondria, lysosomes and produces endoplasmic reticulum stress	[69–74]
NO/cGMP signaling pathway	Cascading reactions mediate allergic symptoms	• The NO/cGMP signaling pathway promotes degranulation of mast cells and triggers nasal venous dilation	[12,66,75]

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measurements.[78] One study demonstrated that intravenous administration of l-NAME, a non-selective nitric oxide synthase inhibitor, to mice with AR reduced nasal congestion symptoms by 80% in the early stage and by 50% in the late stage.[75] Research indicates that NO can stimulate mucin secretion by goblet cells and enhance mucus production in the respiratory tract. Concurrently, the mitotic activity of basal cells is inhibited, leading to damage to the epithelium and its protective functions.[66,67] Alberty et al discovered that in patients with AR, elevated levels of endogenous NO in the nasal ciliated respiratory epithelium promote the regulation of ciliary activity, thereby facilitating mucus clearance.[68] Furthermore, the close association between AR and cellular damage may compromise the nasal epithelial barrier, exacerbating the progression of the disease.[79]

NO/cGMP and AR

The NO/cGMP signaling pathway serves as an essential intracellular signaling system that plays a role in a range of physiological and pathological events. NO binds to the heme group of guanylate cyclase, activating the inactive guanylate cyclase enzyme, which catalyzes the conversion of GTP to cGMP. cGMP plays a significant role in activating specific protein kinases and facilitating protein phosphorylation, which triggers the release of allergic inflammatory mediators from mast cells and other inflammatory cells. This process leads to the activation of nasal mucosa tissues, resulting in allergic symptoms.[12,80] Hiroyasu et al observed that rats suffering from AR exhibited heightened levels of soluble guanylate cyclase (sGC) and PKG in their nasal mucosa, indicating a connection between the NO/cGMP signaling pathway and the dilation of nasal veins in AR.[81]

$ONOO^-$ and AR

The significance of oxidative stress in allergic conditions has received considerable focus. Contact with different air contaminants produces oxygen-derived free radicals and reactive species, including hydrogen peroxide and peroxynitrite.[82] Among these, $ONOO^-$, the product of NO and superoxide anion radical, is a potent oxidizing agent. Research has demonstrated that oxidative stress is a critical factor in AR. In 1999, Kawamoto discovered that iNOS was overexpressed in nasal lavage fluid from patients with AR, leading to increased levels of nitrite and nitrate.[52] Nobuaki et al found that $ONOO^-$ in AR patients induced nasal congestion, and its inhibition can effectively alleviate symptoms.[83] Other studies have indicated that activation of the GATA-3/T-bet pathway and the generation of nitrification stress can induce nasal symptoms in AR mice.[69] Furthermore, pollen in the environment reacts with $ONOO^-$ in the atmosphere, promoting an increase in toll-like receptor 4 (TLR4) associated with the pollen allergen Phleum pratense allergen 5, thereby increasing susceptibility to allergic reactions to such pollens.[84,85] In the potential pathogenesis of AR, nitrosative stress of specific proteins can enhance their immunogenicity. For example, nitration modification of birch pollen allergen latex-like proteins (such as Bet v 1) significantly improves their immunogenicity, which may induce more intense allergic reactions.[70] It is noteworthy that tyrosine-nitrated lipid-binding proteins (such as Der p 2) may not only promote the increase of IgE binding and the enhancement of Th2-type cytokine responses through direct pathways, but also participate in the cascade amplification of allergic symptoms through indirect mechanisms such as aggravating oxidative stress damage and activating the adjuvant-like effects of airway epithelial cells.[71]

In the realm of AR, the primary line of defense consists of the epithelial barrier formed by nasal epithelial cells, essential for safeguarding the host's immune system against detrimental stimuli. $ONOO^-$ can damage organelles such as mitochondria, lysosomes, and the endoplasmic reticulum, leading to cell death.[61] It is thought that the death of epithelial cells in the nasal mucosa may elevate the levels of inflammatory factors, which in turn could worsen the allergic symptoms related to AR.[14] Other studies have indicated that excessive production of $ONOO^-$ may be a key factor contributing to hypoxic stress injury.[86] Although there is no direct evidence of $ONOO^-$ acting on AR cell mitochondria, an increase in mitochondrial oxygen and ROS levels can significantly elevate RNS, leading to mitochondrial damage and further complications.[87] One study found that inhibiting the NOD-like receptor protein 3 (NLRP3) inflammasome can enhance mitochondrial autophagy in the nasal epithelium, improving inflammation in AR mice.[72] Chen et al discovered that mitochondrial fragmentation in the nasal mucosa was significantly increased in AR mice, and the administration of Mdivi-1 (a mitochondrial fission inhibitor) notably reduced nasal symptoms.[13] These findings provide new insights for the treatment of AR.

$ONOO^-$ is a potential regulator of lysosomal proteolysis. Lysosomal injury is a key mechanism of cell death and has significant implications for infection, inflammation, and tumorigenesis.[88,89] AR promotes enhanced autophagy through Der 1 exposure, increased activation of CXCR4, and elevated expression of miR-125b.[73] Impaired AR epithelial barrier function or increased olfactory epithelial autophagy in AR mice occurs through the activation of the AMPK/mTOR pathway, resulting in hypolfactory activity.[90] However, a small amount of lysosomal autophagy does not lead to illness, and lysosomal regeneration can restore the appropriate level of autophagy, preventing excessive loss and the onset of diseases.[91]

$ONOO^-$ also participates in endoplasmic reticulum stress (ERS), disrupting protein folding, transport, and the normal function of glycosylation.[92] The study found that patients with AR exhibit high telomerase gene expression in $CD4^+$ T cells, along with an endoplasmic reticulum (ER) stress response, indicating that ER stress is associated with the development of AR.[74] Liu et al discovered that ERS may promote local IgE production in AR patients, triggering allergic reactions.[93] Other studies have suggested that Jingfang Granules can be regulated by ERS signaling pathways, inhibiting glycolysis and reducing nasal mucous membrane injury and inflammation in mice with AR.[94]

It should be noted, however, that in studies regarding the effects of $ONOO^-$ on mitochondria, endoplasmic reticulum, and lysosomes, the evidence supporting this part of the conclusions mostly comes from animal model studies (Level 3 evidence) and indirect experiments at the cellular level (Level 4 evidence), and direct verification in AR patients has not yet been conducted. Its applicability in the pathological process of human AR and the feasibility of translation into clinical diagnosis and treatment still require further in-depth exploration and confirmation through subsequent studies.

The Impact of AR Treatment on the NO System

Research on the impact of AR therapies on the NO system remains limited, with existing evidence primarily focusing on intranasal corticosteroids, antihistamines, and subcutaneus/sublingual immunotherapy.

In the field of intranasal corticosteroids, studies have confirmed differences in exhaled NO levels among patients with different types of rhinitis. Compared with those with non-allergic rhinitis, AR patients exhibit higher exhaled NO levels, and intranasal glucocorticoids can significantly reduce exhaled NO levels.[95] In a drug comparison study, AR patients were randomly administered antihistamines combined with leukotriene receptor antagonists or intranasal steroids (INS) alone. The results showed that the INS group significantly outperformed the antihistamine plus leukotriene receptor antagonist group in terms of clinical symptom improvement and reduction of nasal NO levels, highlighting the advantage of intranasal steroids in regulating NO levels.[96]

In terms of immunotherapy, relevant studies have also confirmed its regulatory effect on the NO system. For patients who received continuous subcutaneous immunotherapy for 1 year, the study showed that the serum iNOS level and nasal NO content in the effective group of subcutaneous immunotherapy both decreased significantly.[51] In addition, a study on sublingual immunotherapy for AR children by Parisi et al showed that after 6 months of treatment, the number of nasal eosinophils in children decreased significantly, accompanied by a simultaneous decrease in nasal NO content.[97] Overall, compared with the control group, various treatment methods can reduce nasal NO values, among which intranasal steroids are more prominent in improving symptoms and regulating NO levels.

In the field of potential AR drug development, several experimental agents have demonstrated promising potential. Although not yet clinically applied, their mechanisms of action and research data offer new insights for AR therapy: Phosphodiesterase 4 (PDE4) inhibitors exhibit potential advantages in AR treatment by suppressing the hydrolysis of cAMP and cGMP, thereby reducing the release of inflammatory mediators such as histamine and leukotrienes.[98] Additionally, L-arginine, a semi-essential amino acid, is catalyzed by NOS to produce NO in vivo. Inhaled specific arginase inhibitor 2 reduces inflammation-induced iNOS expression while decreasing the production of pro-contractile and pro-inflammatory $ONOO^-$. This mechanism not only prevents NO-overproduction-mediated inflammatory damage but also alleviates nasal mucosal edema via oxidative stress inhibition, providing a dual-regulatory strategy for AR therapy.[99] Although these experimental drugs are not yet in clinical use, the innovativeness of their mechanisms of action offers critical insights for overcoming current limitations in AR therapy. Further clinical studies are warranted to validate their safety and efficacy.

Summary

AR is a major global health concern that has attracted widespread attention. In recent years, its incidence has been on a continuous rise; however, clinical treatment options remain relatively limited, making it urgent to explore new therapeutic ideas and regimens. Existing studies have shown that NO plays a key role in the pathogenesis of AR. In-depth analysis of the pathological mechanism of NO is of great significance for developing new AR therapies and providing more effective treatment options for patients. This review confirms that NO not only directly promotes the progression of AR through nitrosative stress and the NO/cGMP signaling pathway, but also damages nasal epithelial cells during the pathogenesis of AR. Furthermore, it impairs the structure and function of important intracellular organelles such as mitochondria, endoplasmic reticulum, and lysosomes, exacerbating cellular dysfunction and thereby worsening the condition.

Combining NO pathway biology with organelle-targeting strategies opens up a new direction for AR diagnosis and treatment. For diagnosis, exploring the association between key molecules in the NO pathway and markers of damaged organelles enables the development of more specific and sensitive AR diagnostic technologies, which can achieve early and accurate identification of the disease and avoid prolonged illness due to delayed diagnosis. In terms of treatment, by leveraging NO pathway regulation and targeted delivery technology, therapeutic regimens that act precisely on lesion sites can be designed to block pathological damage, repair organelles, enhance therapeutic efficacy, and reduce risks. This will drive the transformation of AR clinical diagnosis and treatment from symptomatic treatment to "precision targeting and mechanism-based intervention", guide researchers to focus on the molecular mechanism of their interaction, provide a basis for the development of new reagents and drugs, and facilitate breakthroughs in AR diagnosis and treatment.

Informed Consent

All authors consent for the publication of the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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