Nitric oxide (NO) has important functions in a variety of physiological and pathophysiological processes in the body, including vasoregulation, haemostasis, neurotransmission, immunity and respiration. The discovery of surprisingly high concentrations of NO in the nasal airway and paranasal sinuses has important implications for the understanding of airway physiology. The high NO levels in the nasal and paranasal airways contribute to the first line defence against microorganisms. Furthermore, autoinhalation of nasal NO may improve pulmonary function and other remote physiological processes. This airborne messenger system represents a new physiological concept of potential clinical importance. However, NO, like several other mediators, has a dualistic function. Airway NO levels are increased in airway inflammations, such as asthma and allergic rhinitis, but is reduced in cystic fibrosis and other conditions with ciliary dysfunction, sinusitis and after exposure to tobacco and alcohol. Consequently, NO may prove valuable as a non-invasive marker in the diagnosis and monitoring of airway pathologies.
Nitric oxide in the nasal airway: a new dimension in otorhinolaryngology.

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Author information

Abstract

The discovery that the gas nitric oxide (NO) is an important signaling molecule in the cardiovascular system earned its Nobel prize in 1998. NO has since been found to play important roles in a variety of physiologic and pathophysiologic processes in the body including vasoregulation, hemostasis, neurotransmission, immune defense, and respiration. The surprisingly high concentrations of NO in the nasal airway and paranasal sinuses has important implications for the field of otorhinolaryngology. NO provides a first-line defense against micro-organisms through its antiviral and antimicrobial activity and by its upregulation of ciliary motility. Nasal treatments such as polypectomy, sinus surgery, removal of hypertrophic adenoids and tonsils, and treatment of allergic rhinitis may alter NO output and, therefore, the microbial colonization of the upper airways. Nasal surgery aimed at relieving nasal obstruction may do the same but would also be expected to improve pulmonary function in patients with asthma and upper airway obstruction. NO output rises in a number of conditions associated with chronic airway inflammation, but not all of them.

Concentrations are increased in asthma, allergic rhinitis, and viral respiratory infections, but reduced in sinusitis, cystic fibrosis, primary ciliary dysfunction, chronic cough, and after exposure to tobacco and alcohol. Therefore, NO, similar to several other inflammatory mediators, probably subserves different functions as local conditions dictate. At present, it seems that the measurement of NO in the upper airway may prove valuable as a simple, noninvasive diagnostic marker of airway pathologies. The objective of this review is to highlight some aspects of the origin, physiology, and functions of upper airway NO, and to discuss the particular methodological problems that result from the complex anatomy.
Nitric oxide and the paranasal sinuses.

Lundberg JO.

Abstract

The discovery within the paranasal sinuses for the production of nitric oxide (NO) has altered the traditional explanations of sinus physiology. This review article reports the ongoing investigation of sinus physiology beginning with the discovery of NO gas production in the paranasal sinuses that occurred in 1995, and the impact that finding has had both in the basic science and clinical arenas. It was shown that healthy paranasal sinus epithelium expresses an inducible NO synthase that continuously generates large amounts of NO, a pluripotent gaseous messenger with potent vasodilating, and antimicrobial activity. This NO can be measured noninvasively in nasally exhaled breath. The role of NO in the sinuses is likely to enhance local host defense mechanisms via direct inhibition of pathogen growth and stimulation of mucociliary activity. The NO concentration in a healthy sinus exceeds those that are needed for antibacterial effects in vitro. In patients with primary ciliary dyskinesia (PCD) and in cystic fibrosis, nasal NO is extremely low. This defect NO generation likely contributes to the great susceptibility to chronic sinusitis in these patients. In addition, the low-nasal NO is of diagnostic value especially in PCD, where nasal NO is very low or absent. Intriguingly, NO gas from the nose and sinuses is inhaled with every breath and reaches the lungs in a more diluted form to enhance pulmonary oxygen uptake via local vasodilation. In this sense NO may be regarded as an "aerocrine" hormone that is produced in the nose and sinuses and transported to a distal site of action with every inhalation.
Nitric oxide (NO) is produced from L-arginine in mammalian tissues. Nitric oxide synthase (NOS) catalyzes this reaction in human tissues. It has been shown that NO serves as an important signaling molecule in the cardiovascular system and is responsible for vasoregulation. In 1991, NO was discovered in exhaled air. More recently, it has been shown that the main production site of exhaled NO is the nose and sinuses. In the upper airways NO upregulates ciliary motility and provides a first-line defense mechanism against microorganisms by antiviral and antimicrobial activity. In the lungs it is involved in ventilation/perfusion matching. Nitric oxide is also a marker for inflammation, with increased nasal output in allergic rhinitis, and a decreased output in sinusitis, nasal polyps and Kartagener's syndrome. This report reviews some aspects of the origin, metabolism, and functions of NO in the upper airways, together with the techniques for, and implications of, nasal NO measurement.
Nitric oxide in upper airways inflammatory diseases.

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Abstract

In the human respiratory tract, the main production sites of exhaled nitric oxide (NO) are the nose and paranasal sinuses. In the upper airways, NO has been suggested to be involved at different levels with regulatory, protective, defensive or deleterious effects. Therefore, we review some aspects of the origin, metabolism, and functions of NO in the upper airways, together with the role of NO in some upper airways inflammatory diseases. Furthermore, we discuss the recent improvements in nasal NO measurements, which may be useful to better characterize the involvement of the NO produced by nose and paranasal sinuses in upper airways inflammatory diseases such as allergic rhinitis, nasal polyposis, sinusitis, primary ciliary dyskinesia, and cystic fibrosis.
Airborne nitric oxide: inflammatory marker and aerocrine messenger in man.

Lundberg JO

Abstract

1. In healthy subjects, exhaled NO originates mainly from the upper airways with only a minor contribution from the lower airways and the lungs. A large NO production takes place in the epithelium of the paranasal sinuses and this NO contributes considerably to the levels of NO found in nasally exhaled air. Immunohistochemical and mRNA in situ hybridisation studies suggest that sinus NO synthase is identical or very closely related to the human iNOS. Furthermore, the NOS activity in sinus mucosa is mostly Ca(2+)-independent. However, the regulation of sinus NOS expression seems to differ fundamentally from what has earlier been described for iNOS. Thus, sinus NOS is constitutively expressed and seems resistant to steroids. The high local NO concentrations in the nasal airways and the sinuses may help to protect against airborne infectious agents. Thus, airborne NO may represent the very first line of defence in the airways, possibly acting on pathogens even before they reach the mucosa. 2. Nasal concentrations of NO are markedly reduced in children with Kartagener's syndrome and in patients with CF. A simple chemiluminescence test could be of help in early non-invasive diagnosis of these chronic airway diseases. 3. Inhaled endogenous NO, derived from the upper airways, may be involved in regulation of pulmonary function in man. NO will reach the lower airways and the lungs with the inspired air and at levels that are especially high during nasal breathing. This NO may act by enhancing blood flow preferentially in well ventilated areas of the lung, thus optimizing ventilation/perfusion matching. The involvement of autogenous NO in regulation of pulmonary function may represent a novel physiological principle, namely that of an enzymatically produced airborne messenger. The term “aerocrine” may be appropriate for this action of NO in the airways. These findings may also help to explain one biological role of the enigmatic human paranasal sinuses, the major sources of NO in the upper airways. 4. A continuous production of NO takes place in the acidic stomach through chemical reduction of nitrite present in swallowed saliva. This is the first evidence of non-enzymatic NO production in humans. Stomach NO may be involved in local defence against swallowed pathogens and in regulation of superficial mucosal blood flow and mucus production. 5. Luminal concentrations of NO are increased in the lower airways of asthmatic children, in the colon of patients with inflammatory bowel disease, and in the urinary bladder of patients with cystitis. Local steroid treatment reduces orally exhaled NO levels in asthmatic children. Nasal NO levels did not differ between controls and asthmatic children with or without concomitant allergic rhinitis. In conclusion, nitric oxide found in exhaled air originates mainly in the upper airways. A large production of NO takes place in the paranasal sinuses from a constitutively-expressed, steroid-resistant “inducible-like” NO synthase in the epithelial cells. Sinus NO contributes substantially to levels of NO found in nasally exhaled air. Sinus NO may have a dual function. First, the very high concentrations in the sinuses may contribute to local host defence. Second, when diluted in the inhaled air, sinus-derived NO may act as an “aerocrine” messenger,
with distal effects on pulmonary blood flow and oxygen uptake. Intubated patients are deprived of autogenous NO from the upper airways and might benefit from substitution. Measurements of local NO production in hollow organs may be done easily by analysing the concentrations of NO gas in luminal air. Such noninvasive methods may be useful not only to explore the role of NO in inflammation and host defence, but also in the diagnosis and monitoring of inflammatory mucosal diseases such as asthma, ulcerative colitis and cystitis. Thus, airborne NO may be looked upon as a marker of inflammation and as an aerocrine messenger in humans.
Inhaled and exhaled nitric oxide.

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Author information

Abstract

Inhaled nitric oxide (NO) is used to treat various cardiopulmonary disorders associated with pulmonary hypertension. The rationale is based on the fact that NO, given by inhalation, only dilates those pulmonary vessels that perfuse well-ventilated lung units. As a result, pulmonary gas exchange is improved while pulmonary vascular resistance is reduced and pulmonary blood flow is increased. Inhaled NO has been successfully applied to treat persistent pulmonary hypertension of the newborn, reducing the need for extracorporeal life support. Although pulmonary hypertension and altered vasoreactivity contribute to profound hypoxaemia in adult and paediatric acute respiratory distress syndrome (ARDS), the benefit of inhaled NO still remains to be established in patients with ARDS. ARDS is a complex response of the lung to direct or indirect insults, leading to pulmonary vasoconstriction and various inflammatory responses. Recent randomized trials suggest that inhaled NO only causes a transient improvement in oxygenation. Whether this effect is important in the long-term management of ARDS remains to be established. NO, measured in the exhaled breath, is an elegant and non-invasive means to monitor inflammation of the upper and lower respiratory tract. In the normal upper airways, the bulk of exhaled NO originates from the paranasal sinuses. Exhaled NO is increased in nasal allergy and decreased in cystic fibrosis, nasal polyposis and chronic sinusitis. That NO production is increased in asthmatic airways is also well established. However, several questions still need to be addressed, in particular evaluation of the sensitivity and specificity of the measurement techniques, and assessment of the bronchodilator action of endogenous NO.
Nitric oxide: a promising methodological approach in airway diseases.

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Author information

Abstract

Nitric oxide (NO) is a potent biological mediator, and has a regulatory role in a wide variety of cellular and tissue functions. In the upper and lower airways, NO has been suggested to be involved in different functions with regulatory, protective, defensive or damaging effects. It is obvious that NO plays an important role in host defense, and is liberated in the nose and the paranasal sinuses. This review aims to highlight some aspects of the origin and function of NO in airway diseases, such as allergic rhinitis, chronic rhinosinusitis with and without nasal polyps, primary ciliary dyskinesia, and cystic fibrosis. In conclusion, NO measurement may be a promising noninvasive diagnostic marker for airway pathologies.