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Science matters

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NO or no NO in asthma?

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Abstract

Nitric oxide (NO) plays a key role as a vasodilator, neurotransmitter, and inflammatory mediator in the airways and is produced in increased amounts in asthma. It may have beneficial effects on airways function as a bronchodilator and is the neurotransmitter of bronchodilator nerves in human airways. On the other hand, NO may have deleterious effects on the airways as a vasodilator by increasing plasma exudation, and may also amplify the asthmatic inflammatory response. Proinflammatory cytokines and oxidants increase the expression of an inducible form of NO synthase (NOS) in airway epithelial cells in asthma, and this may underlie the increased levels of NO found in exhaled air of asthmatic patients. Inducible NOS is inhibited by glucocorticoids, but selective inhibitors of this enzyme may have therapeutic potential in asthma.

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There is increasing evidence that endogenous nitric oxide (NO) plays a key role in physiological regulation of the airways and is implicated in the pathophysiology of airways disease.[1] NO is derived endogenously from the amino acid L-arginine by three forms of the enzyme NO synthase; two constitutive NO synthases (cNOS) are involved in physiological regulation of airways function, and an inducible form of the enzyme (iNOS) is involved in inflammatory diseases of the airways and in host defence against infection. iNOS generates much larger (1000 times) amounts of NO than cNOS and cellular production continues for many hours so that its effects are much more widespread. Immunohistological studies have identified the presence of all three isoforms – endothelial cell NOS (ecNOS), neuronal NOS (nNOS), and inducible iNOS synthases – in human airways. NO has several effects on airway function, and there is increased production of this gas in patients with asthma, as evidenced by increased levels of NO in exhaled air from asthmatic patients.[2] It has both beneficial and detrimental actions on the function of the airways; this conflict may be resolved by considering NO generated by cNOS to be beneficial by mediating local physiological control, whereas the large amounts of NO generated by iNOS may be harmful by amplifying the inflammatory response.

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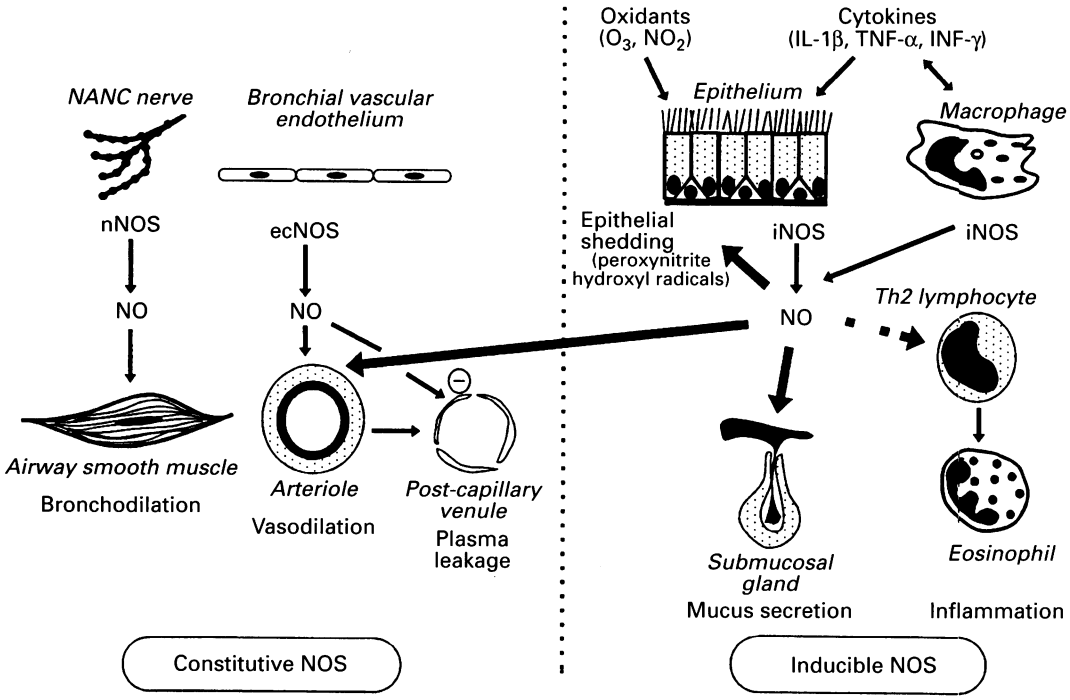
Scientific basis

INCREASED NO PRODUCTION IN ASTHMA

The mechanism for increased production of NO in asthma has now been elucidated. Biopsy samples from asthmatic patients show increased iNOS expression by immunocytochemistry in epithelial cells.[3] Cultured human airway epithelial cells show iNOS expression after exposure to proinflammatory cytokines such as interleukin 1β and tumour necrosis factor α, both of which are produced in asthmatic airways.[4] Epithelial cells also express iNOS after exposure to oxidants via the activation of the transcription factor nuclear factor kappa B (NF-κB),[5] which is critical for transcription of the iNOS gene. This may be relevant in the inflammatory response to atmospheric pollutants such as ozone and nitrogen dioxide. NO may also be derived from macrophages or other inflammatory cells, although this has yet to be demonstrated directly. Exhaled levels of NO are increased in patients with asthma[2] and increase even further during the inflammatory late response to allergen.[6]

BENEFICIAL EFFECTS OF NO

NO mediates the non-adrenergic non-cholinergic neural inhibitory responses in human airways[7] and acts as a "braking" mechanism to cholinergic bronchoconstriction (figure).[8] This suggests that NO derived from the neuronal form of NO synthase should be beneficial in patients with asthma and that blocking this enzyme would increase bronchoconstriction. Surprisingly, inhaled NO is relatively ineffective as a bronchodilator.[9] This may be because it does not reach airway smooth muscle due to inactivation. In experimental animals NOS inhibitors increase the bronchoconstrictor response to histamine and bradykinin, suggesting that NO is normally protective, although inhalation of NOS inhibitors in asthmatic patients has no effect on airway tone.[10] Endogenous NO may also be important in regulating



Nitric oxide (NO) generated from neuronal NO synthase (nNOS) in non-adrenergic non-cholinergic (NANC) nerves relaxes airway smooth muscle. NO generated by endothelial NOS (ecNOS) and inducible NOS (iNOS) may dilate bronchial vessels and this may increase plasma leakage and oedema. The high concentrations of NO generated by iNOS induction by cytokines and oxidants in airway epithelial cells (and possibly macrophages) may result in vasodilatation, plasma exudation, mucus secretion, and indirect activation of T helper 2 (Th2) lymphocytes, thus increasing asthmatic inflammation. This suggests that selective inhibition of iNOS may be beneficial in asthma.

mucociliary clearance since an NOS inhibitor decreases ciliary beat frequency in airway epithelial cells.[11] Low concentrations of NO may also inhibit plasma exudation.

HARMFUL EFFECTS OF NO

NO is important in non-specific host defence of the respiratory tract and has toxic effects on bacteria, viruses, and parasites.[12] It is involved in the inflammatory response to infection, which is likely to be beneficial, but in the context of asthma the same inflammatory response is deleterious, resulting in increased symptoms and airways obstruction. NO is a potent vasodilator in the bronchial circulation and may mediate the hyperaemia seen in asthmatic airways. Endogenous NO may increase the exudation of plasma by increasing blood flow to leaky post-capillary venules, thus increasing airway oedema, and this has been demonstrated experimentally.[1] Generation of high concentrations of NO may also cause vasodilation of the pulmonary vessels resulting in ventilation-perfusion mismatch. NO may also increase mucus secretion directly or via an increase in blood flow to submucosal glands.

Eosinophilic inflammation in asthma is driven by helper T lymphocytes (Th2) that secrete interleukin 5 (IL-5). NO may amplify asthmatic inflammation by selective inhibition of T lymphocytes that secrete interferon γ (Th1 cells), as interferon γ suppresses the proliferation of Th2 cells. This would allow expansion and secretion of Th2 lymphocytes which secrete IL-5.[12] NO generated by iNOS in airway epithelial cells combines avidly with superoxide anions generated by inflammatory cells in the airways to form peroxynitrite ions that may have inflammatory effects directly and through the generation of toxic hydroxyl radicals that may contribute to airway epithelial shedding in asthma (figure).

Therapeutic potential

NO donor compounds relax human airways in vitro, raising the possibility that such compounds may be useful as novel bronchodilators. However, the major problem with this class of drug is the cardiovascular side effects which limit the dose that can be given, as NO has a greater relaxant effect on vascular than on airway smooth muscle. The balance of evidence suggests that NOS inhibition may have a beneficial effect on asthmatic airways. Glucocorticoids inhibit induction of iNOS (by blocking NF-κB) in epithelial cells[4] and reduce the increased exhaled NO in asthmatic patients to normal[10]; this action of steroids may contribute to their beneficial effect in asthma. Non-selective NOS inhibitors such as N^G-monomethyl-L-arginine (L-NMMA) given in a single dose by inhalation to normal and asthmatic subjects reduce exhaled NO without any effect on airway or cardiovascular function,[10] suggesting that endogenous NO is unlikely to be important in regulating airways function even in patients with asthma. More prolonged administration of NOS inhibitors would be needed to assess their anti-inflammatory potential. In experimental models of other inflammatory diseases, such as arthritis and glomerulonephritis, NOS inhibitors are effective in reducing the inflammation. However, non-selective inhibitors are unlikely to be useful

clinically as they result in systemic hypertension. Thus, therapeutic approaches will depend upon the development of selective iNOS inhibitors and such drugs are currently in development.

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