Guanylyl cyclases, nitric oxide, natriuretic peptides, and airway smooth muscle function

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Hamad, Ahmed M., Andrew Clayton, Baharul Islam, and Alan J. Knox. Guanylyl cyclases, nitric oxide, natriuretic peptides, and airway smooth muscle function. Am J Physiol Lung Cell Mol Physiol 285: L973–L983, 2003; 10.1152/ajplung.00033.2003.—Airway smooth muscle (ASM) plays an important role in asthma pathophysiology through its contractile and proliferative functions. The cyclic nucleotides adenosine 3',5'-cyclic monophosphate (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP) are second messengers capable of mediating the effects of a variety of drugs and hormones. There is a large body of evidence to support the hypothesis that cAMP is a mediator of the ASM's relaxant effects of drugs, such as ß2-adrenoceptor agonists, in human airways. Although most attention has been paid to this second messenger and the signal transduction pathways it activates, recent evidence suggests that cGMP is also an important second messenger in ASM with important relaxant and antiproliferative effects. Here, we review the regulation and function of cGMP in ASM and discuss the implications for asthma pathophysiology and therapeutics. Recent studies suggest that activators of soluble and particulate guanylyl cyclases, such as nitric oxide donors and natriuretic peptides, have both relaxant and antiproliferative effects that are mediated through cGMP-dependent and cGMP-independent pathways. Abnormalities in these pathways may contribute to asthma pathophysiology, and therapeutic manipulation may complement the effects of ß2-adrenoceptor agonists.

atrial natriuretic peptide; guanosine 3',5'-cyclic monophosphate; asthma

RECENT STUDIES HAVE SHOWN that both nitric oxide (NO) and atrial natriuretic peptide (ANP) have a significant bronchodilator effect in asthmatic subjects. Because NO and ANP share a common intracellular second messenger mechanism (i.e., cGMP), this suggests that cGMP may have important regulatory functions in human airway smooth muscle (ASM). Guanylyl cyclases (GC) are the enzymes that catalyze the conversion of GTP to guanosine cGMP and exist as soluble and particulate membrane-associated enzymes. NO is the natural activator of soluble GC, and a large part of this review will focus on its functions. Recent studies showed that carbon monoxide and pituitary adenylate cyclase-activating peptide can also activate soluble GC and relax guinea pig airways in vitro (15, 16, 110), but these are not discussed in detail here. Particulate GC act as plasma membrane receptors for natriuretic peptides and related peptides. Several membrane forms of the enzyme have been identified up to now. Some of them serve as receptors for the natriuretic peptides, a family of peptides that includes ANP, brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), three peptides known to play important roles in renal and cardiovascular physiology. The type of GC present varies from tissue to tissue. In some tissues, the concentration of the soluble GC to particulate GC is nearly equal, whereas in others, such as the small intestine, the particulate form predominates (23). In some organs, such as the kidney, the relative abundance of both forms varies throughout the organ (22). However, the relative expression of different isoforms of GC in the lung have not been studied directly. This review will discuss the importance of cGMP as a second messenger in ASM, focusing on recent studies of soluble and particulate GC activators in intact and cultured ASM in vitro and in asthmatic subjects in vivo.

NO AND SOLUBLE GC

NO synthesis from the semiessential amino acid L-arginine is catalyzed by a family of enzymes called nitric oxide synthases (NOS). There are at least three isoforms of NOS that have been cloned and sequenced (37, 72, 83). There are two constitutive isoforms (constitutive NOS [cNOS]): the endothelial isoform (endothelial NOS) or type III NOS, normally present in endothelial cells, and the neuronal isoform (neuronal
NO donors may lead to loss of beneficial effects of cGMP in airway smooth muscle (ASM), namely relaxation and inhibition of proliferation. Proinflammatory asthma mediators, cytokines

PKC activation

Desensitization of particulate GC

Desensitization of soluble GC

Decreased cGMP formation

Impaired ASM relaxation and enhanced proliferation

Fig. 1. Theoretical mechanisms whereby desensitization of guanylyl cyclases (GC) might contribute to asthma pathophysiology. Proinflammatory cytokines and mediators in the asthmatic airways activate protein kinase C (PKC), which in turn desensitizes the particulate GC in airway smooth muscle (ASM). Proinflammatory cytokines and mediators may also induce inducible nitric oxide (NO) synthase (iNOS), which produces NO in excess amounts. This excess NO desensitizes soluble GC in ASM. Desensitization of either form of GC will lead to loss of the beneficial effects of cGMP in ASM, namely relaxation and inhibition of proliferation.
with this, NOS inhibition enhances agonist responses in guinea pig trachea with intact mucosa but not in epithelially denuded preparations (34, 87). Moreover, bradykinin increased cGMP and relaxed guinea pig trachea with intact epithelium but contracted epithelium-denuded trachea, suggesting that bradykinin stimulated the release of NO from the tracheal epithelium that in turn elevated cGMP levels and caused relaxation (34, 128). Studies in bovine trachea showed that NOS inhibition increased the basal tone, abolished histamine-induced increase in NO release from the epithelial layer, and enhanced histamine-induced contraction (107). More recent studies showed that repeated antigen exposure led to bronchial hyperresponsiveness in guinea pigs, probably due to a lack of EpDRF-mediated bronchodilatation (74). Indeed, clinical studies with NOS inhibitors in asthmatic subjects support this notion (99, 100). Furthermore, a recent study using human bronchial strips showed that the antiasthmatic effect of ginsenoside, an extract of Panax ginseng,  

Table 1. Effects of soluble/particulate GC activators on ASM in vitro in different species

<table>
<thead>
<tr>
<th>Activator, Species</th>
<th>Effect Referene</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP, atriopeptins, SNP</td>
<td>Relaxation of both basal and agonist-induced tone (14, 38, 47, 96, 125)</td>
</tr>
<tr>
<td>BNP, CNP</td>
<td>Relaxation (117, 118)</td>
</tr>
<tr>
<td>S-nitrosothiols</td>
<td>Relaxation (59)</td>
</tr>
<tr>
<td>ANP</td>
<td>Reverse and protect against methacholine-induced tone (6, 19, 85)</td>
</tr>
<tr>
<td>ANP, atriopeptins, SNP</td>
<td>Relaxation of agonist-induced tone (ANP &gt; SNP); no effect on basal tone (57, 58)</td>
</tr>
<tr>
<td>SIN-1, SNP, SNAP</td>
<td>Relaxation (19, 78, 106, 107)</td>
</tr>
<tr>
<td>Nitrovasodilators</td>
<td>Relaxation and increased cGMP (93, 129)</td>
</tr>
<tr>
<td>SNP, NO</td>
<td>Relaxation and increased cGMP (116)</td>
</tr>
<tr>
<td>ANP, SNP</td>
<td>Reverse and protect against methacholine-induced tone (6, 20, 84)</td>
</tr>
<tr>
<td>S-nitrosothiols, SNP, NO, SIN-1</td>
<td>Relaxation and increased cGMP (30, 36, 123, 124)</td>
</tr>
<tr>
<td>ANP, BNP, CNP, SNP, SNAP</td>
<td>Increased cGMP (peptides &gt; NO donors) (45)</td>
</tr>
<tr>
<td>ANP, SNAP, SNP</td>
<td>Homologous desensitization of GC (46)</td>
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<tr>
<td>ANP, SNP, SNAP</td>
<td>Inhibition of proliferation (42)</td>
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<tr>
<td>SNP, SNAP</td>
<td>Increased cGMP formation (29)</td>
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GC, guanylyl cyclases; ASM, airway smooth muscle; ANP, atrial natriuretic peptide; SNP, sodium nitroprusside; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide; SIN-1, 3-morpholinosydnonimine; NO, nitric oxide; SNAP, S-nitroso-N-acetyl penicillamine.

Table 2. Effects of soluble/particulate GC activators on ASM function in vivo in different species

<table>
<thead>
<tr>
<th>Activator, Species</th>
<th>Effect Referene</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNAP, NO</td>
<td>Reversing methacholine-induced bronchoconstriction &gt; basal tone (29)</td>
</tr>
<tr>
<td>Infused ANP</td>
<td>Reverse and protect against agonist-induced bronchoconstriction but not compliance (31)</td>
</tr>
<tr>
<td>Infused ANP, BNP, CNP</td>
<td>Reverse antigen-induced changes in lung resistance (88)</td>
</tr>
<tr>
<td>Infused ANP</td>
<td>Reverse methacholine-induced changes in lung resistance but not compliance; no effect on baseline lung function (9)</td>
</tr>
<tr>
<td>Inhaled NO</td>
<td>Reverse methacholine-induced increase in lung resistance but not compliance (49)</td>
</tr>
<tr>
<td>Inhaled NO, 80 ppm</td>
<td>Increased sGaw in asthmatic subjects but not in normal and COPD patients (50)</td>
</tr>
<tr>
<td>Inhaled NO, 80 ppm</td>
<td>Reverse methacholine-induced changes in sGaw in healthy men; no effect on basal sGaw (109)</td>
</tr>
<tr>
<td>Inhaled NO, 100 ppm</td>
<td>Small increase in FEV; and FVC (but not FEF20) after methacholine-induced bronchoconstriction (63)</td>
</tr>
<tr>
<td>Inhaled nitroglycerine</td>
<td>Bronchodilation (104)</td>
</tr>
<tr>
<td>Inhaled isosorbide dinitrate</td>
<td>Reverse exercise-induced bronchoconstriction; no effect on baseline lung function (121)</td>
</tr>
<tr>
<td>Infused nitroglycerine</td>
<td>Mild improvement in FEV; in mild asthma but no change in FEV, FVC in acute severe asthma (38, 66, 76, 90)</td>
</tr>
<tr>
<td>Sublingual nitrates</td>
<td>Bronchodilation, increased plasma CDPG levels in moderately severe asthmatics, but higher doses were required to reduce airflow resistance in normal and mild asthmatics (2, 17, 52, 53)</td>
</tr>
<tr>
<td>Infused ANP</td>
<td>Bronchodilation of FN, FVC in acute severe asthma (13)</td>
</tr>
<tr>
<td>Inhaled ANP</td>
<td>Bronchodilation, increased plasma CDPG levels in moderately severe asthmatics, but higher doses were required to reduce airflow resistance in normal and mild asthmatics (38, 66, 76, 90)</td>
</tr>
<tr>
<td>Infused ANP</td>
<td>Bronchodilation of FN, FVC in acute severe asthma (2, 17, 52, 53)</td>
</tr>
<tr>
<td>Inhaled ANP</td>
<td>Protection against direct and indirect bronchial challenges (51, 73)</td>
</tr>
<tr>
<td>Inhaled ANP</td>
<td>Protect against subsequent bronchial challenge. Higher doses (5 mg) produced significant bronchodilation (3, 55, 56)</td>
</tr>
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COPD, chronic obstructive pulmonary disease; ppm, parts per million; sGaw, specific conductance; FEV, forced expiratory volume; FVC, forced vital capacity; FEF, forced expiratory flow.
Panax ginseng is via stimulation of NO generation from airway epithelium and cGMP synthesis (119).

NO may also be produced endogenously by iNANC nerves and act locally on ASM. The iNANC mechanism is the only known neural bronchodilator pathway in humans, and NO is the only known neurotransmitter of iNANC nerves in humans (10, 11, 30, 124). In vitro studies in human airway preparations showing that the iNANC response is associated with a selective increase in cGMP and that selective inhibition of cGMP-specific PDE enzyme enhances the iNANC response are consistent with it being mediated by NO-induced increases in cGMP (32, 124).

In vivo studies in different species, including humans, showed a bronchodilator effect for inhaled NO. Hogman and colleagues (50) showed that inhalation of 80 parts per million of NO increased the specific airway conductance in asthmatic subjects, although to a lesser extent than after β2-agonists. These findings were confirmed in subsequent studies (63, 109). Clinical trials with nitrovasodilators generally showed a weak bronchodilator effect, with the inhaled route being the most promising method of delivery. However, most studies report significant cardiovascular side effects (38, 76, 90).

The relaxant effect of NO in different species correlates well with cGMP elevation, suggesting a causal role for cGMP in mediating its relaxation (36, 57, 129). However, other work in ASM suggests alternative mechanisms may also operate, including direct activation of maxi-K+ channels (1), oxidation of intracellular contractile proteins, e.g., myosin head or regulatory proteins involved in contraction (64, 95), or decreased sensitivity to intracellular Ca2+ (91, 98). This was clarified in a recent study comparing the effects of two redox forms of NO, NO- [liberated by SNAP] and NO• [liberated by 3-morpholinosydnonimine (SIN-1)], in human main stem bronchi and canine trachealis (60). The results of this study suggest that NO• causes release of internal Ca2+ in a cGMP-independent fashion, leading to activation of the maxi-K+ channels and relaxation, whereas NO- relaxes the airways through a cGMP-dependent, Ca2+-independent pathway.

Proliferation. Although there is evidence to support a role for the NO-GC-cGMP pathway in the regulation of proliferation in other cell systems, including vascular smooth muscle (111), it was not known until recently whether NO has a similar role in ASM. We have shown that SNAP, a direct NO donor, inhibited the proliferation of cultured HASMC in response to serum and thrombin (42). The antiproliferative effect of NO in our study was likely to be cGMP mediated based on the fact that zaprinast, a selective NO•-inhibitor, enhanced this effect and that a cell-permeable cGMP analog (8-bromoguanosine 3',5'-cyclic monophosphate) also had an antiproliferative effect. Additional cGMP-independent mechanisms for NO's antiproliferative effect were suggested by the fact that cGMP analogs had a weaker effect than NO donors. A subsequent study looking at the mechanisms underlying the antiproliferative effect of NO in HASMC showed that NO inhibited proliferation in both G1 and S phases of the cell cycle (44). The G1 phase effect was cGMP dependent, whereas the S phase effect was due to cGMP-independent inhibition of ribonucleotide reductase (Fig. 2). More recently, the proliferative effects of endothelin-1 (ET-1), both alone and in combination with epidermal growth factor, and the effect of NO on the cell proliferation were investigated in cultured guinea pig bronchial smooth muscle (67). A NO donor, SIN-1, reduced the cell-proliferative effect of ET-1 in a concentration-dependent manner. A soluble GC inhibitor partly, but significantly, reversed the effect of SIN-1. Studies using NOS inhibitors have shown that HASMC express type I NOS and inhibition of NOS enhances DNA synthesis and cell proliferation (92).

NATRIURETIC PEPTIDES AND PARTICULATE GC

The natriuretic peptide family of hormones has an important role in salt and water homeostasis. The human natriuretic peptides include ANP, BNP, and CNP. At first, the sole source of ANP was thought to be the heart. It has been known for a long time that ANP is secreted from the atrial myocytes into the blood stream in response to distension or stretch of the atrial wall (105). Several more recent studies, however, show that the lung is another source of ANP in different species, including humans (7, 71, 108, 114). Studies in hamsters showed that the ANP gene is expressed mainly in the airway epithelium and smooth muscle, and, to a lesser extent, in the alveolar wall, muscular media of the pulmonary arteries, and extraparenchymal pulmonary veins (86). ANP and the other natriuretic peptides act on different particulate GC receptors. These are transmembrane proteins composed of a single transmembrane domain, a variable extracellular natriuretic peptide-binding domain, and a more conserved intracellular kinase homology domain (KHDK and catalytic domain. GC-A, the receptor for ANP and BNP, also named natriuretic peptide receptor-A or -1, has been studied widely. Its mode of activation by peptide ligands and mechanisms of regulation serve as prototypes for understanding the function of other particulate forms of GC. Activation of this enzyme by its ligand is a complex process requiring oligomerization, ligand binding, KHD phosphorylation, and ATP binding. Gene knockout and genetic segregation studies have provided strong evidence for the importance of GC-A in the regulation of blood pressure and heart and renal functions (68). Immunohistochemical studies have localized GC-A to the ASM and alveoli in bovine lung (65). However, specific receptors for ANP have not been sought directly in human lung. We have used pharmacological tools to characterize the presence of these receptors in cultured HASMC (45). In this study, we showed that treatment of HASMC with ANP, BNP, and CNP led to a time- and concentration-dependent increase of cGMP levels in these cells, suggesting that particulate GC is expressed in these cells. The order of potency seen in our experiments was: ANP > BNP > CNP, consistent with type A and B of...
particulate GC being present in these cells (GC-A > GC-B). Although heat-stable enterotoxin (GC-C ligand) did not affect cGMP over the time course of our experiments, suggesting that GC-C is not expressed in HASMCs, a recent study showed that treatment of guinea pigs with uroguanylin (a ligand of GC-C receptor in gastrointestinal tissue) significantly inhibited leukotriene C4-induced pulmonary changes in a dose-dependent manner (89). The disparity between this study and ours may reflect species differences.

DESENSITIZATION OF PARTICULATE GC

Similar to soluble GC, particulate GC may undergo homologous desensitization after prolonged exposure to ANP through a cGMP-independent mechanism (46). We further studied the mechanism of particulate GC desensitization in HASMC (43); pretreatment of HASMC with phorbol 12-myristate 13-acetate (PMA), a protein kinase C (PKC) activator, led to time- and concentration-dependent desensitization of ANP-stimulated cGMP accumulation. GF-109203X, a selective PKC inhibitor, blocked the PMA-induced desensitization but did not block ANP-induced desensitization. In addition, desensitization by PMA and ANP showed an additive effect.

WHAT ARE THE BIOLOGICAL EFFECTS OF PARTICULATE GC ACTIVATORS ON ASM FUNCTION?

Contraction. ANP has a direct relaxant effect associated with cGMP accumulation in guinea pig airway in vitro (24, 75, 125). BNP and CNP have similar effects in guinea pig airway preparations (117, 118). ANP is a potent relaxant of the intrinsic tone as well as tone induced by various agonists in guinea pig trachea.
(95, 125). However, it may be more effective in relaxing methacholine- than in leukotriene D4-induced tone (46). In rat tracheal tissue, atriopeptins cause a weak relaxation of intrinsic tone as well as carbachol-induced tone (33). In bovine tracheal smooth muscle, ANP and atriopeptins have a direct relaxant effect on the tone induced by various agonists (57, 58). The potency of ANP was intermediate between isoprenaline and SNP. Infused ANP has been shown to reverse and protect against agonist-induced bronchoconstriction in guinea pigs in vitro (31, 88). Similar results were shown in sheep (9). More recently, BNP and CNP were reported to have a similar effect as ANP on antigen-induced changes in lung resistance in sensitized guinea pigs; the rank of order of inhibitory potency was BNP = ANP > CNP (88).

ANP also relaxes human airways in vitro. ANP was reported to reverse and protect against methacholine-induced contraction of human bronchi (6, 20, 84). ANP was more potent than SNP and salbutamol (20). Data from human and guinea pig airways suggest that the ANP relaxant effect may be due to cGMP-dependent activation of large conductance Ca2+-activated K+ channel (24, 75). A number of studies have looked at the effect of ANP on lung function in both normal and asthmatic subjects in vivo. Infused ANP at a concentration producing plasma levels in the pathophysiological range had a significant bronchodilator effect in asthmatic subjects in vivo. Infused ANP at a concentration producing plasma levels in the pathophysiological range had a significant bronchodilator effect in asthma (52). The effect of infused ANP was similar to that of nebulized β2-agonists, although it was shorter lived. High dose-inhaled ANP produced less bronchodilator effect compared with intravenous ANP (3, 55, 56). This can be explained by the rapid degradation of ANP by the neutral endopeptidases (NEP) within the airways (6). This was confirmed in a subsequent study in which NEP inhibition greatly enhanced the bronchodilator effect of ANP in asthmatics (4, 5).

However, it was observed that short-term exercise and acute asthma were associated with a rise in the plasma level of ANP (54, 103), suggesting that ANP could have a physiological role in the regulation of the bronchomotor tone. This increase in ANP may be due to hypoxia-induced pulmonary vasoconstriction, leading to increased right atrial pressure (127).

**Proliferation.** As with NO, ANP inhibits proliferation in several cell lines, but until recently, its role in regulation of HASMC proliferation was not known. We have shown that human ANP1–28 (a GC activator), rat ANP (rANP)104–126 (which binds selectively to the ANP clearance receptors without elevating cGMP), and a cGMP analog had an antiproliferative effect in HASMC, suggesting that both cGMP-dependent and cGMP-independent mechanisms are involved in ANP's antiproliferative effect (42). Although we found that the human ANP1–28, like SNAP, had antiproliferative effects, it produced a smaller maximum effect. This difference in efficacy contrasts with relative abilities of ANP and SNAP to elevate cGMP (ANP > SNAP). This paradox suggests that compartmentalization of cGMP pools may enable cGMP generated by soluble GC to have a greater effect than that generated by particular GC.

The lung is capable of synthesizing ANP (35, 41, 86), and both types of ANP receptors (GC-linked and clearance receptors) have been characterized and localized throughout the lung. In the heart, where more is known about the function of ANP, ANP release is stretch stimulated (28). Similarly, Springall et al. (115) suggested that stretch of rat pulmonary vein stimulates ANP release. Preliminary data support a similar stretch-dependent mechanism for ANP release in tracheal muscle of anesthetized sheep (93). Stretch-dependent release of ANP from ASM, occurring with deep inspiration, could lead to cGMP elevation with subsequent inhibition of ASM tone and proliferation.

**CROSS TALK BETWEEN CGMP AND CAMP PATHWAYS**

The other main cyclic nucleotide involved in ASM relaxation is cAMP, which is activated mainly by β2-adrenoceptor agonists (69). In the classic pathway, β2-adrenoceptor agonists bind to β2-receptors, which are coupled to adenylyl cyclase, leading to production of cAMP. cAMP then activates protein kinase A (PKA), and PKA phosphorylates a number of substrates to bring about its intracellular effects (94, 113). In parallel pathways, NO and ANP activate soluble and particulate GC, respectively, to produce cGMP, and cGMP activates protein kinase G (PKG), which then phosphorylates its own set of substrates (94, 113, 120). It has become clear, however, that the situation is much more complex, and although it has not been studied in detail in ASM, cross talk between cGMP and cAMP pathways is well recognized in many other biological systems (94, 113). This cross talk can occur at a number of levels.

First, cyclic nucleotides can repress the degradation of their counterparts through their actions on PDEs (120). For example, the cGMP-stimulated PDE-2 and the cGMP-inhibited PDE-3 preferentially hydrolyze cAMP (94, 113, 120). Both of these PDE isozymes are present in human airway smooth muscle (120). Second, cGMP and cAMP are both capable of cross-activating their respective kinases. For example, at physiological concentrations, both cGMP and cAMP can activate PKG in vascular smooth muscle (21). In contrast, in the same experiments, PKA was only activated by cAMP. Other investigations have, however, shown that cGMP can inhibit proliferation of cultured vascular smooth muscle by activating PKA (26). In contrast, cAMP relaxes pig coronary arteries via PKG (62). Third, both PKG and PKA have a number of common substrates. Sites of phosphorylation in ASM for PKA include phospholipase C, maxi-K+ channels, Na+–K+–ATPase, myosin light chain kinase, and sarcoplasmic reticulum Ca2+ pumps. PKG can phosphorylate maxi-K+ channels and Ca2+ uptake pumps in ASM, and in non-ASM cells, contractile proteins and phospholipase C can also be phosphorylated (reviewed in Ref. 69). There is also evidence that PKA and PKG may cooperatively phosphorylate some substrates such that phosphorylation...
by one kinase changes the conformation of the target protein, making serine threonine sites more accessible to the other kinase (94). Alternatively, PKG or PKA may regulate the activity of protein phosphatases, which then modifies the effect of the other kinase (94). Finally, cross talk in some systems occurs in the regulation of cGMP/cAMP synthesis (77).

Although cross talk can be complex, compartmentalization within the cell of the enzymes catalyzing cyclic nucleotide synthesis and degradation, the enzymes responsible for cyclic nucleotide-mediated phosphorylation and the protein targets of these kinases exert a degree of constraint and allows cell specificity in the interactions and functional responses (94).

Collectively, these studies suggest there is considerable potential for pathways activated by NO donors or natriuretic peptides to enhance the effects of β2-adrenoceptor agonists either on relaxation or proliferation of ASM. Further studies addressing possible interactions in vitro may be of great interest. The demonstration of an additive effect of NO and NO donors on β2-agonist-induced bronchodilation in asthmatic subjects (50, 104) and that a combination of ANP and salbutamol evokes a greater effect than either alone in reversing and protecting against methacholine-evoked contraction in isolated human bronchi (84) suggest that such combinations could be of benefit in the treatment of asthma, allowing lower doses of each individual drug to be used.

**RELEVANCE OF GC TO ASTHMA**

The evidence reviewed thus far suggests that both soluble and particulate GC may have important roles in asthma pathophysiology but that NO donors and natriuretic peptides act through a combination of cGMP-dependent and cGMP-independent effects. NO donors and natriuretic peptides have ASM relaxant properties that may be important under different physiological circumstances. NO produced by NO donors and natriuretic peptides may act specifi cally to block muscarinic cholinergic receptors. The demonstration of an additive effect of NO donors and β2-agonists, in some studies, suggests that such combinations could be of benefit in the treatment of asthma, allowing lower doses of each individual drug to be used. An alternative strategy might be to utilize S-nitrosylated derivatives of existing bronchodilator molecules. Interestingly, it was shown that S-nitrosylated derivatives of vasoactive intestinal peptide preserve the intrinsic function of vasoactive intestinal peptide but acquire NO-like vasoactivity when tested on aortic rings (61). Similar studies in the airways would be interesting. Currently, there is a great deal of interest in developing PDE inhibitors with a more favorable pharmacological profile than existing agents. The combined use of PDE inhibitors and GC activators could allow the use of smaller doses of both (32). It is also possible that the transient effects of ANP could be prolonged either by the concomitant use of NEP inhibitors or pharmacological modification of the ANP molecule.

Besides its relaxant effect, NO may also protect against airway remodeling by inhibiting ASM proliferation (an important component of airway thickening in asthma). Dysfunction of GC activation by endogenous stimuli may contribute to the bronchial hyperresponsiveness characteristic of asthma as asthmatic inflammation results in excess production of NO (Fig. 1). This excess NO would be expected to cause desensitization of soluble GC in ASM. Furthermore, activation of PKC as a result of asthmatic inflammation could desensitize particulate GC and impair cGMP production in response to endogenous natriuretic peptides (Fig. 1).

In conclusion, the GC/cGMP second messenger system has a parallel role to the adenyl cyclase/cAMP system in ASM, regulating its contractile and proliferative functions. Drugs activating this pathway have the potential to be new antiasthma therapies that could be used in conjunction with existing drugs.
REFERENCES


