Airway smooth muscle relaxation

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Bronchodilators are important agents in the treatment of asthma and chronic obstructive airways disease. Beta agonists, theophyllines, and antimuscarinic agents are the main drugs in current use, but others are under investigation. Although other actions may be important, these drugs produce bronchodilation either by a direct effect on airway smooth muscle or by inhibiting neural pathways. As our understanding of airway smooth muscle relaxant mechanisms increases, new therapeutic possibilities are being realised. Several recent findings contradict established dogma— for example, the assumption that β agonists and theophyllines act solely via cyclic adenosine monophosphate (cAMP)-linked intracellular pathways has been questioned and studies with atrial natriuretic peptide and nitrates suggest that cyclic guanosine monophosphate (cGMP) may be an important relaxant second messenger. The role of potassium channel activators is being explored with the development of drugs which relax airway smooth muscle by a direct action on cell membrane ion channels. In this review we discuss what is known of the likely mechanisms of action of the airway smooth muscle relaxants in current use and their effects on calcium homeostasis, and suggest how developments in our understanding of relaxant mechanisms may aid the development of treatment for airways obstruction in the future. Agents such as the muscarinic, histamine or leukotriene antagonists which cause bronchodilatation by blocking the effects of neurotransmitters or mediators at the receptor level are not discussed, nor are the effects other than those on airway smooth muscle of bronchodilators in current use.

Role of calcium in relaxation of airway smooth muscle

The drugs in current use cause relaxation of airway smooth muscle by stimulating a cyclic nucleotide second messenger system, predominantly cAMP and cGMP, by inhibiting the breakdown of cyclic nucleotides or by a direct action on cell membrane ion channels or transporters (table 1, fig 1). Since the relation between an increase in intracellular calcium and contraction is well established, it is generally assumed that relaxation is preceded by a fall in intracellular calcium, although relatively few studies have investigated this. A fall in intracellular calcium (measured by aequorin luminescence) accompanied isoprenaline-induced relaxation in canine trachealis contracted with 5-hydroxytryptamine or cholinergic agonists and, since the fall in intracellular calcium correlated strongly with the reduction in tension, it was thought to be responsible. A fall in cellular calcium was also seen in cAMP-mediated relaxation in canine airway smooth muscle and in cGMP-mediated relaxation in canine and bovine airway smooth muscle. There was no fall in intracellular calcium in response to β agonist in bovine tracheal smooth muscle in one study, and in some studies increases in intracellular calcium in response to β agonists have been seen as a result of calcium influx through membrane channels under resting conditions. The inconsistencies seen in these studies may be due to the fact that the experiments which failed to show a reduction in calcium were carried out at 22°C when many intracellular processes, including Na+/K+ ATPase, would be inhibited. On balance it seems likely that a fall in intracellular calcium is associated with relaxation in the same way that an increase in intracellular calcium is associated with contraction.

Table 1 Agents known to cause airway smooth muscle relaxation in vitro

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Agents</th>
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<tbody>
<tr>
<td>1. Agents acting through stimulating cAMP</td>
<td>β agonists, vasoactive intestinal peptide, peptide histidine isoleucine, pituitary adenylate cyclase activating peptide PGE2, PGI2</td>
</tr>
<tr>
<td>2. Agents acting through stimulating cGMP</td>
<td>Nitric oxide, nitrosothiols</td>
</tr>
<tr>
<td>3. Inhibitors of cAMP, GMP breakdown</td>
<td>Nitrates, sodium nitroprusside</td>
</tr>
<tr>
<td>4. Ion channels</td>
<td>ANP, BNP, CNP</td>
</tr>
<tr>
<td>5. Miscellaneous</td>
<td>Potassium channel activators, sodium channel/transport modulators, cyclic nucleotide phosphodiesterase inhibitors</td>
</tr>
</tbody>
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Figure 1. Main pathways of airway smooth muscle relaxation: (1) via receptors linked to cAMP; (2) via receptors linked to cGMP; (3) PDE (phosphodiesterase) inhibition; (4) activation of K+ channels; (5) inhibition of Ca2+ channels. AC = adenylate cyclase; PKA = protein kinase A; GC = guanylate cyclase; PKG = protein kinase G.
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Figure 2. The main calcium removal mechanisms in airway smooth muscle: (1) Ca\textsuperscript{2+} Mg\textsuperscript{2+} ATPase; (2) Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger which is linked to (3) Na\textsuperscript{+}/K\textsuperscript{+} ATPase; and (4) Ca\textsuperscript{2+} uptake by intracellular stores.

At least three calcium removal mechanisms are thought to lower intracellular calcium in airways smooth muscle: (1) calcium magnesium ATPase, (2) sodium-calcium exchange, and (3) uptake of calcium into intracellular organelles such as sarcoplasmic reticulum and mitochondria (fig 2).

**CALCium MAGNesIUM ATPASE (CALCium EFFLUX PUMP)**

The electroneutral calcium efflux pump found in the plasma membrane of most cells including smooth muscle\textsuperscript{3} is a magnesium- and ATP-dependent enzyme which extrudes one calcium ion for two hydrogen ions. It is stimulated by a calcium-calmodulin complex which may act as a feedback mechanism to limit the rise in intracellular calcium following stimulation.\textsuperscript{4-10} Its activity also depends on the activity of AMP-dependent protein kinases in several types of smooth muscle,\textsuperscript{11} although the only study to date on airway smooth muscle failed to show this.\textsuperscript{12}

**SODIUM-CALCIUM EXCHANGE**

The sodium-calcium exchanger transports one calcium ion for three sodium ions and is driven by the sodium gradient across the membrane which, in turn, is maintained by Na\textsuperscript{+}/K\textsuperscript{+} ATPase.\textsuperscript{13} Although there is good evidence for sodium-calcium exchange in cardiac muscle,\textsuperscript{14} its presence in smooth muscle is less well established.\textsuperscript{15} Such a mechanism probably exists in the airways since reducing external sodium causes contraction of canine,\textsuperscript{16} bovine,\textsuperscript{17,18} and human airway smooth muscle in vitro, and ion flux studies suggest that Na\textsuperscript{+}/Ca\textsuperscript{2+} exchange sites are abundant in bovine tracheal smooth muscle.\textsuperscript{20}

**INTRACELLULAR CALCIUM REMOVAL MECHANISMS**

The sarcoplasmic reticulum and mitochondria are the most important intracellular organelles for the removal of calcium. The sarcoplasmic reticulum accumulates calcium via a cAMP-dependent mechanism.\textsuperscript{5,12,22} The mitochondria take up calcium, store it as a non-ionic calcium-phosphate complex, and release it back into the cytosol via a calcium efflux pathway.\textsuperscript{23} The mitochondrial calcium store may protect the cell against calcium overload in pathological conditions,\textsuperscript{7} at least in cardiac muscle.

**Cyclic AMP-mediated relaxant mechanisms**

The cAMP pathway is the most important relaxant signal transduction pathway in airway smooth muscle. The β\textsubscript{2} adrenoceptor, the main receptor studied with respect to this pathway, is coupled through an intermediary stimulatory G protein (G\textsubscript{s}) to adenylate cyclase which catalyses the intracellular conversion of ATP to cAMP. Adenylyl cyclase can also be inhibited through muscarinic M\textsubscript{3} receptors via an inhibitory G protein (G\textsubscript{i}). cAMP activates a group of cyclic AMP-dependent protein kinases (protein kinase A) which, in turn, phosphorylate a number of different substrates which then cause relaxation. The precise way in which cAMP causes relaxation is still not clear. Several actions of cAMP-dependent protein kinases which can cause relaxation have been identified (fig 3). These include inhibition of inositol phosphate hydrolysis,\textsuperscript{23,24} increased calcium uptake by internal stores,\textsuperscript{25} inactivation of myosin light chain kinase,\textsuperscript{26} and activation of cell membrane ion channels and transporters such as K\textsuperscript{+} channels\textsuperscript{27} and Na\textsuperscript{+}/K\textsuperscript{+} ATPase.\textsuperscript{28,29} The net effect of these processes would be to reduce intracellular calcium concentration and increase contractile protein phosphorylation, thereby producing relaxation. Although protein kinase A has been shown to produce effects at these sites in vitro, the relative importance of each mechanism in mediating the relaxant effects of β adrenoceptor agonists in vivo is still unclear. Recent work in porcine and ferret airway smooth muscle suggests that β agonists can produce relaxation independently from elevation of cAMP via stimulation of the GTP binding protein of adenylate cyclase (G\textsubscript{s}) coupled to maxi-K\textsuperscript{+} channels.\textsuperscript{30} The effect of G\textsubscript{i} and protein kinase A on the maxi-K\textsuperscript{+} channel is additive.\textsuperscript{31}

Agents which act through stimulation of cAMP production include β\textsubscript{2} adrenoceptor agonists, vasoactive intestinal peptide and prostaglandins.

Figure 3. Schematic representation of the sites of phosphorylation for protein kinase A. The combined effects of phosphorylation at these sites is to lead to airway smooth muscle relaxation. MLCK = myosin light chain kinase; SR = sarcoplasmic reticulum; PLC = phospholipase C; DAG = diacylglycerol; Ins P\textsubscript{3} = inositol trisphosphate; PIP\textsubscript{3} = inositol bisphosphate; G = guanosine nucleotide binding protein; AC = adenylate cyclase.
\( \beta_2 \) adrenoceptor agonists

Beta\(_2\) agonists increase intracellular cAMP levels\(^{31}\) and are potent relaxants of airway smooth muscle in several species including man.\(^{32}\) The negative log molar EC\(_{50}\) value for isoprenaline-induced relaxation of bronchial smooth muscle spontaneous tone is in the range of 9 to 7,\(^{33}\) with lower values (7 to 3 indicating reduced potency) being seen when tissue is preconstricted with contractile agents such as histamine or acetylcholine. Most \( \beta_2 \) selective agonists such as salbutamol are partial agonists when compared with isoprenaline, which is a full but non-selective \( \beta_2 \) agonist in vitro. The effects of \( \beta_2 \) agonists in vitro can be mimicked by direct activators of adenylate cyclase such as forskolin.

The new \( \beta_2 \) adrenoceptor agonists, formoterol and salmeterol, produce more potent and prolonged relaxation of guinea pig trachea and human bronchial smooth muscle in vitro than drugs such as salbutamol.\(^{33,34}\) The negative log molar EC\(_{50}\) values for relaxation of human bronchial smooth muscle is 9-6 for formoterol and 7-6 for salmeterol.\(^{35}\) Both drugs are more lipophilic than salbutamol and it has been postulated that non-specific binding to the cell membrane or binding to an exoreceptor may prolong their action.\(^{36}\) Salmeterol is a partial agonist compared with both isoprenaline and salbutamol.\(^{37}\)

Vasoactive intestinal peptide (VIP)

VIP immunoreactivity has been demonstrated in nerve fibres in the airway\(^{38}\) and VIP receptors have been identified on airway smooth muscle.\(^{38}\) VIP relaxes airway smooth muscle from several species including human airways and is a potent bronchodilator.\(^{39}\) Its effect on human airways is enhanced by epithelial removal and peptidase inhibition.\(^{40}\) Part of its action may be due to Na\(^+\)/K\(^+\) ATPase activation since relaxation in rabbit airway smooth muscle is inhibited by the Na\(^+\)/K\(^+\) ATPase inhibitor ouabain.\(^{41}\)

Prostaglandins

Prostaglandin E\(_2\) (PGE\(_2\)) relaxes canine airway smooth muscle.\(^{28}\) In human airway smooth muscle at low concentrations it increases cAMP via adenylate cyclase\(^{39}\) and causes relaxation, whereas at higher concentrations it causes contraction.\(^{42,44}\) This can probably be explained by its actions on different receptors.\(^{45}\) The contractile effects of prostaglandins are thought to be mediated by thromboxane receptors at which PGE\(_2\) is a weak agonist. There are three prostaglandin E receptors – EP\(_1\), EP\(_2\), and EP\(_3\) – which are coupled to different cell signalling systems. The relaxant effect of PGE\(_2\) is thought to be due to stimulation of the EP\(_3\) receptor which is coupled to cAMP. PGI\(_2\) and beraprost (a PGI\(_2\) analogue) also cause relaxation of canine airway smooth muscle which can be inhibited by inhibitors of adenylate cyclase, suggesting that cAMP pathways are involved.\(^{46}\)

Cyclic GMP relaxant mechanisms (figs 1, 4)

It has become clear that cGMP produced by guanylate cyclase is also a relaxant second messenger in airway smooth muscle.\(^{46}\) Guanylate cyclase exists in two forms – a soluble and a particulate form – both of which have been purified and characterised.\(^{47,48}\) Soluble guanylate cyclase is a haem protein which exists as a heterodimer composed of two subunits; it is activated by nitric oxide and the nitro group of vaso/bronchodilators. Particulate guanylate cyclase is one of the receptors mediating the effects of atrial natriuretic peptide.\(^{49,50}\) Guanylate cyclase catalyses the conversion of GTP to cGMP which then activates a group of distinct cGMP-dependent protein kinases. Considerable sequence homology exists between cGMP-dependent protein kinases and other kinases, particularly cAMP-dependent protein kinases.\(^{51}\) In contrast to cAMP-dependent protein kinases which are the major intracellular effector system for cAMP, many cGMP effects are not due to cGMP-dependent protein kinases, at least in non-muscle cells. cGMP-dependent protein kinases appear to have various sites of action in airway smooth muscle as with cAMP-dependent protein kinases (fig 4)\(^{51,55}\).

The agents which act through stimulation of cGMP production include nitrates and atrial natriuretic peptide.

Nitrates

Glyceryl nitrate, sodium nitroprusside and the cell permeable cGMP analogue, 8-bromo-
cGMP, have been shown to relax canine and bovine airway smooth muscle\textsuperscript{56-58} and, in the case of sodium nitroprusside, human airway smooth muscle.\textsuperscript{59} S-nitrosothiols, which consist of nitric oxide linked to a thiol group and are found endogenously in airway secrections, relax guinea pig and human airway smooth muscle.\textsuperscript{60} Dissolved nitric oxide gas relaxed bovine tracheal rings in one study.\textsuperscript{61} Endogenous nitric oxide and S-nitrosothiols are produced by cells such as airway epithelium and non-adrenergic non-cholinergic nerves and may be involved in the regulation of bronchomotor tone (fig 5).\textsuperscript{62} This effect might, however, be offset by pro-inflammatory actions of nitric oxide.\textsuperscript{62}

ATRIAL NATRIURETIC PEPTIDE
Atrial natriuretic peptide (ANP) relaxes guinea pig\textsuperscript{60} and bovine\textsuperscript{60} airway smooth muscle and this is associated with increased cGMP\textsuperscript{63} in bovine airway smooth muscle. ANP is degraded rapidly by epithelial peptidases and the response to ANP is enhanced by removing epithelium or adding a peptidase inhibitor.\textsuperscript{65} The effects of ANP appear to be less marked in human airway smooth muscle.\textsuperscript{66-68} Two related peptides, brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), have been shown to increase cGMP and relax guinea pig airway smooth muscle, but have not been studied in man.\textsuperscript{69,70}

Agents preventing the breakdown of cAMP and cGMP
A family of phosphodiesterase enzymes hydrolyse the 3'-phosphoester bond on cAMP and cGMP converting them to their inactive 5'-nucleotide metabolites 5'-AMP and 5'-GMP. Theophylline and other xanthine derivatives cause airway smooth muscle relaxation in vitro and bronchodilatation in vivo, and although they may have other mechanisms of action, phosphodiesterase (PDE) inhibition appears to be important for smooth muscle relaxation.\textsuperscript{71} Theophylline has been shown to relax smooth muscle from several species including man when contracted with a wide range of spasmogens in vitro,\textsuperscript{72} although it is some 1000 times less potent than isoprenaline in relaxing human bronchi contracted by moderate doses of carbachol.\textsuperscript{73} Theophylline is a rather non-selective inhibitor of tissue phosphodiesterases and this is one factor underlying its narrow therapeutic index.

Recent studies have identified at least seven classes of PDE isoenzymes, each of which has several isoforms (table 2). These isoenzymes vary in their tissue distribution and their ability to break down cAMP and cGMP.\textsuperscript{74,75} Airway smooth muscle contains several PDE isoenzymes in most species and in human airway smooth muscle types III, IV and, to a lesser extent, V are important for relaxation.\textsuperscript{76-79} Drugs which inhibit specific isoenzymes may be relatively tissue selective in their effects and thus have advantages over theophylline. Studies of some of the more specific type IV inhibitors are currently under investigation in man.

Drugs acting on cell membrane ion transport
CALCIUM CHANNEL ANTAGONISTS
Voltage-dependent calcium channel agonists such as verapamil, gallopamil, nifedipine, and nifedipine inhibit the contractile response to depolarising agents and to various spasmogens (histamine, cholinergic agonists, leukotriene D\textsubscript{4}) in isolated airway smooth muscle from several species including man.\textsuperscript{80-84} They also reduce the response of sensitised guinea pig and human airway smooth muscle to antigen,\textsuperscript{85,86} the order of potency for this effect being nifedipine >verapamil >diltiazem. The effects of the drugs in vitro have generally been modest even with high drug concentrations; this may be because the initiation of airway smooth muscle contraction is due to

![Figure 5](image-url)
Mechanisms whereby K⁺ channel activation is thought to produce airway smooth muscle relaxation. SR = sarcoplasmic reticulum.

Figure 6


K⁺ channel activators

POTASSIUM CHANNEL ACTIVATORS

The electrical stability of airway smooth muscle is controlled by K⁺ channels. The two which have generated the most interest with respect to airway smooth muscle relaxation are the maxi-K⁺ channel and the ATP-regulated channel (fig 6). Activation of K⁺ channels causes membrane hyperpolarisation in airway smooth muscle.

CALCIUM ACTIVATED CHANNELS (MAXI-K)

The large conductance K⁺ channels (maxi-K) found in airway smooth muscle from several species including man are activated by calcium and inhibited by charybdotoxin. Maxi-K⁺ channels may have a role in both cAMP and cGMP-mediated airway smooth muscle relaxation. The channels are activated by cAMP-dependent protein kinase in rabbit trachea and directly by cAMP in porcine and ferret trachea and, when inhibited by charybdotoxin, cAMP-mediated relaxation of guinea pig and human airway smooth muscle and cGMP-mediated relaxation in bovine airway smooth muscle are inhibited. Functional antagonism could be responsible for these inhibitory effects, however. Charybdotoxin can cause calcium influx through voltage-dependent calcium channels, and the inhibitory effect of charybdotoxin on isoprenaline-induced relaxation in guinea pig trachea is inhibited by nifedipine.

METABOLICALLY CONTROLLED CHANNELS

ATP-sensitive K⁺ channels open in response to a reduction in ATP and K⁺ channel activators (cromakalim, nicorandil, pinacidil) and are blocked by the sulphonylureas (glibenclamide, tolbutamide, chlorozolesamide). K⁺ channel activators have been shown to relax spontaneous tone and contraction induced by histamine, prostaglandin D₃, and leukotriene C₄ in guinea pig airways, and histamine and cholinergic tone in human airways. K⁺ channel openers are very effective at reducing spontaneous tone in human airway smooth muscle but less effective at reversing receptor-mediated contraction.

The mechanisms by which K⁺ channel activators cause airway smooth muscle relaxation are uncertain but are likely to include (a) membrane hyperpolarisation with reduction of calcium influx via voltage-dependent calcium channels; (b) activation of Na⁺/K⁺ ATPase causing a decrease in intracellular Na⁺ and, as a consequence, Ca²⁺ efflux via Na⁺/Ca²⁺ exchange; and (c) possibly the regulation of intracellular calcium release (fig 6).

The drugs currently available lack specificity for the airways and, although some bronchodilatation has been seen in patients with asthma, systemic side effects such as hypotension have been a problem.

SODIUM

Smooth muscle contains several exchangers which regulate intracellular sodium including the Na⁺/Ca²⁺ exchanger, Na⁺/K⁺ ATPase, and the Na⁺/H⁺ antiport. Intracellular sodium is closely linked to intracellular calcium through the Na⁺/Ca²⁺ exchanger, so changes in intracellular sodium or in sodium exchange systems can affect relaxation. The Na⁺/H⁺ antiport may also alter the contractile status of the cell by regulating intracellular pH. Activation of Na⁺/K⁺ ATPase reduces intracellular sodium causing an increase in calcium efflux via Na⁺/Ca²⁺ exchange. There is evidence that activation of Na⁺/K⁺ ATPase is important for drugs which act through cAMP such as β agonists, but not those that act through cGMP. Na⁺/K⁺ ATPase activity is increased by protein kinase A but not protein kinase G in canine airway smooth muscle membrane particulates and inhibition of Na⁺/K⁺ ATPase with ouabain inhibits the relaxant responses to drugs that act through cAMP such as nitroprusside. Activators of Na⁺/K⁺ ATPase or Na⁺/Ca²⁺ exchange would therefore be expected to act as airway smooth muscle relaxants. No such agents are currently available.

Amlodipine, a non-specific inhibitor of sodium channels and transport processes including Na⁺ entry channels, Na⁺/H⁺ and Na⁺/Ca²⁺ exchange, relaxes airway smooth muscle tone and inhibits receptor-operated contraction in canine and bovine trachealis and the response to antigen in guinea pig airways in vitro. Further studies suggest that this effect may be due to inhibition of Na⁺ entry channels or protein kinase C rather than inhibition of Na⁺/H⁺ exchange or Na⁺/Ca²⁺ exchange. Inhaled amlodipine caused no bronchodilatation, however, in one study of normal and asthmatic subjects.
Miscellaneous
These are several other post-receptor sites where drugs could modify the relaxant processes in airway smooth muscle including guanosine nucleotide regulatory proteins (G proteins), calcium uptake into intracellular stores, and enzymes regulating the contractile process such as calmodulin, protein kinase C, and myosin light chain kinase. Few agents which affect these processes have been studied. Calmodulin antagonists have been shown to inhibit contraction in response to antigen in guinea pig trachea, but in general these agents lack specificity. The putative protein kinase C inhibitors H-7 and staurosporine inhibit contractile responses to spasmsgens in guinea pig and bovine airway smooth muscle, but the drugs lack specificity and have other effects such as inhibition of myosin light chain kinase.

Lithium, which inhibits myosininositol phosphate leading to depletion of membrane phospholipid pools, causes relaxation and protects against histamine-induced contraction in guinea pig airways in vitro. Lithium also reduces the airway response to histamine in asthmatic subjects.

Some anaesthetic agents such as the benzodiazepines, halothane, and ketamine have been shown to relax airway smooth muscle in various animal species. This may be relevant for the treatment of acute asthma in intensive care units.

Conclusion
The pharmacology of airway smooth muscle is complex due to the wide range of effects of receptors and ion channels on airway smooth muscle cells and the complex post-receptor mechanisms involved in the contractile and relaxant responses. This provides a wide range of potential sites for pharmacological agents to produce relaxation of airway smooth muscle.

Of the established smooth muscle relaxant drugs, β2 adrenergic agonists are currently the most useful. Advances are being made in several areas, however. Modifications to the structure of β2 adrenergic agonists have produced agents with a longer duration of action. Identification of different isoforms of phosphodiesterase and the development of selective isoenzyme inhibitors may produce drugs which can exert tissue selectivity by acting on these enzymes present in airway smooth muscle tissue but no other tissues. This might prevent some of the undesirable side effects seen with non-selective phosphodiesterase inhibitors such as theophylline.

Ion channel inhibitors or activators have proved disappointing therapeutic agents to date. Although the calcium channel antagonists have relaxant properties in vitro, they have not proved useful in vivo. The potassium channel activators have additional properties to inhibition of calcium entry via voltage-dependent calcium channels but greater specificity for airway smooth muscle is needed if they are to be useful relaxant agents.

A number of other steps in the contractile and relaxant responses are open to targeting by pharmacological agents, including modulation of G proteins, the inositol phospholipid cascade and calcium release mechanisms, calmodulin and protein kinase C. There is also potential for drugs which facilitate calcium extrusion across the cell membrane by activating sodium-calcium exchange, sodium potassium ATPase, or calcium magnesium ATPase.

Airway smooth muscle pharmacology is an exciting and developing area for which the future holds much promise.

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