

Phosphodiesterase inhibitors: Lily the Pink's medicinal compound for asthma?

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Abstract

The second messenger cyclic nucleotides, cyclic AMP and cyclic GMP, mediate relaxation of airways smooth muscle and suppression of multiple inflammatory cell functions. The intracellular concentrations of these cyclic nucleotides are regulated by a superfamily of phosphodiesterase (PDE) enzymes which break down cAMP and cGMP and, thereby, affect airway tone and inflammation. Theophylline and other drugs that act through inhibition of PDE are currently the subject of great research interest, since the uncovering of their anti-inflammatory actions suggests a possible additional mode of action in inflammatory diseases such as asthma. The characterisation of multiple families of PDE isoenzymes with distinct tissue distributions has encouraged hope that selective PDE inhibitors can be developed which act at specific targets without exhibiting the side effects of non-selective inhibitors like theophylline. The combination of bronchodilator and anti-inflammatory properties in a single drug by selective inhibition of specific PDE isoenzymes could produce agents most efficacious in every way for asthma therapy.

(Thorax 1996;51:647-649)

Keywords: phosphodiesterase inhibitors, airway smooth muscle, inflammatory cells.

If the volume of reports appearing in the scientific and medical literature is a reliable gauge, inhibitors of cyclic nucleotide phosphodiesterase (PDE), like Lily the Pink's Medicinal Compound*, would seem to be most efficacious in every way for the treatment of asthma. Demonstrations of the actions of new, highly selective PDE inhibitors, and even of less selective inhibitors such as theophylline, on airways smooth muscle and on the inflammatory cells implicated in the pathophysiology of diseases such as bronchial asthma, are published almost

weekly; several of these drugs are now undergoing clinical trials.¹ The motive for this research effort is the desire to develop drugs that combine the bronchodilator actions of β_2 adrenoceptor agonists with a prophylactic action against the inflammatory processes that render the airways hyperreactive. The involvement of the cyclic nucleotide, adenosine 3',5'-cyclic monophosphate (cAMP), in the intracellular actions of β agonists has long been established and PDE inhibition was adopted as an alternative approach to elevating cAMP levels while bypassing the complications of receptor downregulation and subsensitivity in severe episodes of bronchoconstriction.² Similarly, the well established relationship between increased levels of cAMP and suppression of inflammatory cell function is a possible target for therapeutic interventions in inflammatory diseases, including asthma.³ Recent reports of immunomodulatory actions of low doses of theophylline – the archetypal PDE inhibitor – suggest that the clinical benefits of theophylline may be underlain by combined bronchodilator and anti-inflammatory attributes.^{4,5} While this work has renewed interest in theophylline, the prospects for drugs that selectively and potently inhibit one or two PDE isoenzymes are also the object of some excitement among asthma researchers.

Scientific basis

PDEs form seven families of isoenzymes, some of which include multiple proteins coded by distinct genes.^{1,3} The development of selective inhibitors for these families and, more recently, even for individual isoenzymes within a family,⁶ has allowed precise identification of the PDE activities in cells involved in airway disease processes and investigation of the pharmacology of their inhibitors.

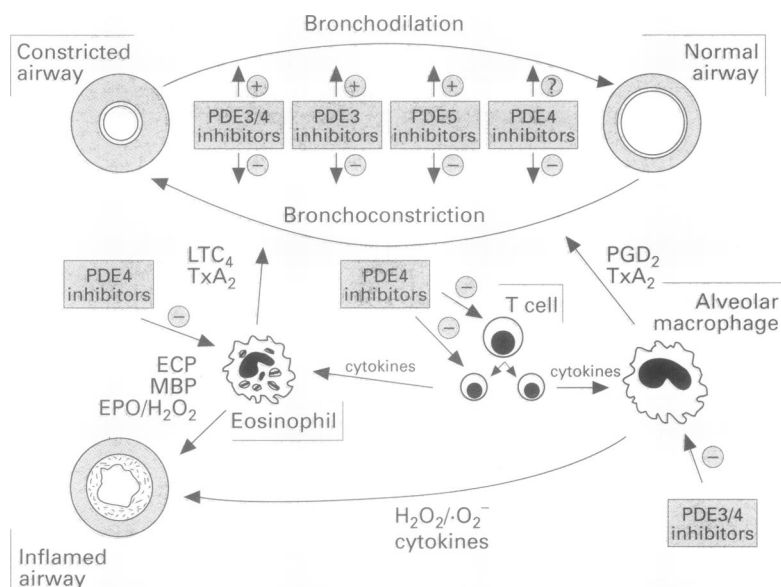
PDE INHIBITORS AND AIRWAYS SMOOTH MUSCLE
Human airways smooth muscle contains isoenzymes of the PDE1, 2, 3, 4 and 5 families; there is evidence for the expression of multiple forms of PDE1 and PDE4 in these tissues³ and reverse transcriptase/polymerase chain reaction (RT-PCR) procedures have revealed the ex-

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* Readers born before 1940 may wish to substitute Auntie Maggie's Homemade Remedy. Readers outside the UK should not worry.



Targets for inhibitors of phosphodiesterase (PDE) isoenzymes in inflammatory airways disease. The isoenzymes present in each cell type are listed in the text. The actions of selective PDE inhibitors are indicated: + = positive effect (? = very weak action); - = inhibition; ECP = eosinophil cationic protein; EPO = eosinophil peroxidase; H_2O_2 = hydrogen peroxide; LT = leukotriene; MBP = eosinophil major basic protein; $\cdot O_2^-$ = superoxide anion radical; PG = prostaglandin; Tx = thromboxane.

pression of four different genes for PDE4 isoforms in lung and tracheal smooth muscle.¹ In vitro, relaxation of airways can be achieved with selective inhibitors of the cAMP-specific enzymes, PDE3 and PDE4 (figure), although their potency appears to depend upon the agent used to contract the tissues and the degree of tone.³ Selective inhibitors of PDE5 – which preferentially hydrolyses guanosine 3',5'-cyclic monophosphate (cGMP) – are also capable of relaxing airway smooth muscle (figure) but are less effective than PDE3 or 4 inhibitors.³ Simultaneous inhibition of PDE3 and PDE4 – either with two separate drugs, such as siguazodan and rolipram, or with a combined PDE3/PDE4 inhibitor such as zardaverine – is the most effective means of relaxing bronchial tone.^{3,7}

Theophylline inhibits all PDE isoenzymes in human bronchus with similar potency⁸ and relaxes resting or precontracted bronchi in vitro.^{7,8} The fact that certain isoenzyme-selective inhibitors are substantially more potent than theophylline, both in inhibiting their respective enzymes and in relaxing airway smooth muscle preparations in vitro, has led to a hope that these drugs – particularly combined PDE3/PDE4 inhibitors – might prove effective as bronchodilators in vivo. Studies of selective inhibitors have shown PDE4 selective drugs to have bronchospasmolytic actions in dogs and guinea pigs. Selective PDE3 inhibitors are more potent than PDE4 selective drugs in dogs but are associated with cardiovascular side effects. PDE5 and mixed PDE3/4 inhibitors also reverse bronchoconstriction in guinea pigs.³

PDE INHIBITORS AND INFLAMMATORY CELLS

The distribution of PDE isoenzymes in inflammatory cells has been extensively studied

in recent years. A general characteristic of these cells is the presence of PDE4, although some contain various additional isoenzymes with differing functional roles.³ Eosinophils, which are widely believed to contribute to the pathophysiology of asthma, contain only PDE4⁹ – which also predominates in neutrophils³ – and monocyte PDE is also accounted for primarily or exclusively by PDE4.^{3,10} Eosinophils, neutrophils and monocytic cell lines have been shown by RT-PCR to express three of the four PDE4 subtypes.¹ In contrast to monocytes, alveolar macrophages contain significant PDE5 and PDE3 activities as well as high PDE1 activity.¹¹ T lymphocytes contain predominantly PDE4 but also some PDE3 and a small amount of PDE5 activity.¹² Human mast cells have not been extensively studied to date but basophils contain mostly PDE4, with minor PDE5 and PDE3 activities.³

Selective PDE4 inhibitors, particularly rolipram, as well as non-selective drugs such as theophylline, have been found to suppress inflammatory functions – including oxygen radical generation, arachidonic acid metabolism, and secretion of granule proteins and cytokines – in eosinophils (figure), neutrophils, and monocytes.^{1,3,10} In alveolar macrophages, however, PDE4 inhibitors have little effect on oxygen radical generation or cytokine release, although some suppression of cell function can be seen with combined PDE3/4 inhibition¹¹ or with non-selective inhibition by theophylline (figure).¹ T lymphocytes, which orchestrate immune responses, exhibit reduced proliferation and cytokine secretion following treatment with a selective PDE4 inhibitor, although the suppressive effect of rolipram on T cell proliferation is enhanced when PDE3 is also inhibited with SKF 94120.¹ The role of PDE in B lymphocytes is poorly characterised but IgE secretion from mononuclear cells has been shown to be reduced by treatment with a PDE4 inhibitor, Ro 20-1724, even though cAMP is suggested to promote class switching in favour of IgE production.¹ This discrepancy may be accounted for by an indirect, T cell or monocyte-mediated action.

Prolonged elevation of intracellular cAMP levels leads to upregulation of PDE4 in human monocytic cell lines.^{3,6,10} This change may have important implications for asthma, since regular use of adrenoceptor agonists could be responsible for depressing sensitivity of leucocytes to cAMP-elevating hormones and mediators by accelerating the breakdown of cAMP.³ Recent studies have identified PDE4D as the major gene product whose expression is augmented by cAMP,^{6,10} so that inhibitors with selectivity for this individual isoenzyme may prove important in asthma therapy.

Therapeutic potential

To date, clinical studies with isoenzyme-selective PDE inhibitors have not produced promising results, probably owing to short treatment periods.¹⁻³ Most clinical trials have been performed using dual PDE3/PDE4 inhibitors with the aim of maximising both

bronchodilator and anti-inflammatory actions. Side effects are associated with inhibition of both of these enzymes, however,^{1,3} and the doses that can be used safely may be restricted to levels that are insufficient to exert significant therapeutic actions. As understanding of the expression and regulation of individual PDE isoenzymes advances, more selective drugs should become available that act potently and specifically on certain target cells and cell functions, so that effective doses can be administered without the risk of excessive cardiac, renal, and central nervous system side effects.

Conclusion

Although PDE isoenzymes are the object of great scientific interest, the development of inhibitors for the enzymes may remain of limited clinical importance for some time since most of the isoenzyme families are ubiquitous. The identification of subtypes of PDE within the families presents more narrowly defined targets for potential therapeutic actions of new inhibitors, although "third generation" PDE inhibitors, specific for a single subtype, are in their infancy. Should their potential be realised, with the modulation of defined target cell functions becoming achievable, medicinal

compounds most efficacious in every way might be a reality for the treatment of asthma.

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