

Cyclic nucleotide phosphodiesterases

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Cyclic nucleotide second messengers (cAMP and cGMP) play a central role in signal transduction and regulation of physiologic responses. Their intracellular levels are controlled by the complex superfamily of cyclic nucleotide phosphodiesterase (PDE) enzymes. Continuing advances in our understanding of the molecular pharmacology of these enzymes has led to the development of selective inhibitors as therapeutic agents for disease states ranging from cancer and heart failure to depression and sexual dysfunction. Several PDE types have been identified as therapeutic targets for immune/inflammatory diseases. This article briefly reviews the available *in vitro*, pre-clinical, and clinical data supporting the potential for selective PDE inhibitors as immunomodulatory agents. (J Allergy Clin Immunol 2001;108:671-80.)

Key words: Cyclic AMP, cyclic GMP, cyclic nucleotide phosphodiesterase, immunosuppression, inflammation

The social use of phosphodiesterase (PDE) inhibitors, such as caffeine, dates back several millennia; their continued popularity is suggested by the fact that 3 of the top 25 most valued brand-name companies on the world market are purveyors of caffeinated beverages.¹ The medicinal use of PDE inhibitors can be traced to the work of Henry Hyde Salter in his monograph of 1860 entitled "On asthma: Its pathology and treatment." In that work, Salter recommends the administration of "two breakfast cups of strong coffee . . . given on an empty stomach" as a remedy that "in many cases is more efficacious than any other." Interestingly, such a dosing regimen would optimize absorption, achieve high peak serum levels, and specifically target the exaggerated diurnal variation in pulmonary function characteristic of asthma.² However, it was not until 1957 that our mechanistic understanding of cyclic nucleotides and PDEs began to evolve. In that year, Sutherland and Rall^{3,4} first described the properties

Abbreviations used

AC:	Adenylyl cyclase
AKAP:	A kinase anchor proteins
cAK:	cAMP-dependent protein kinase
cAMP:	Adenosine 3', 5'-cyclic monophosphate
cGK:	cGMP-dependent protein kinase
cGMP:	Guanosine 3', 5'-cyclic monophosphate
GC:	Guanylyl cyclase
LT:	Leukotriene
PDE:	Phosphodiesterase

of a cyclic adenine ribonucleotide (later called *adenosine 3', 5'-cyclic monophosphate* [cAMP]), its formation in response to epinephrine and glucagon, and inhibition of its hydrolysis by sodium fluoride and caffeine. As the importance of cyclic nucleotide second messengers in cellular signaling and homeostasis became evident over the ensuing decades, pharmacologic regulation of this pathway by PDE inhibitors became an area of both academic and pharmaceutical industry research. In the 1970s, 2 separate observations focused this research effort on immune/inflammatory diseases. First, in a series of reports by Lichtenstein and colleagues, the immunomodulatory properties of cAMP and the anti-inflammatory potential of PDE inhibitors were demonstrated.⁵⁻⁷ Second, several groups demonstrated that PDE activity from tissue homogenates could be fractionated into pharmacokinetically and biologically distinct PDE subtypes and that the relative amounts of these PDEs varied among different tissues.⁸⁻¹⁰ Thus the superfamily of PDE enzymes was born and the potential utility of selective PDE inhibitors to target specific tissues, pathways, and disease processes was first postulated.

This year marks the 30th anniversary of the description of cAMP as an immunomodulator. The superfamily of PDEs has burgeoned to 14 subtypes and more than 50 distinct isoforms. Several selective PDE inhibitors have been marketed; several others have gained notoriety for their toxicities. Clinical trials of selective PDE inhibitors continue, but the therapeutic promise of selective PDE inhibitors for inflammatory diseases is yet to be realized. The structural chemistry and molecular biology of PDEs have been reviewed elsewhere.^{11,12} This article will update our understanding of the classification and pharmacology of PDEs and the *in vitro* and *in vivo* evidence for immunomodulatory activity associated with inhibition of specific PDE subtypes.¹³

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CLASSIFICATION AND STRUCTURAL BIOLOGY

Table I shows the current classification scheme for cyclic nucleotide PDEs. Eleven distinct families (or types) are differentiated functionally on the basis of substrate specificity and sensitivity to endogenous/exogenous regulators and genetically on the basis of sequence homology (3 additional families have been reported, but the data available at this time are insufficient for their inclusion in Table I).¹³⁻¹⁷ Most of the families include more than 1 gene product (subtype, designated with a letter following the family number—eg, PDE4D). Multiple splice variants (isoforms, designated with a number following the subtype letter—eg, PDE4D1), each with different functional and regulatory characteristics, may exist for any given gene product.^{18,19} The number of specific human PDEs is thus well over 50. Several of the more commonly used selective inhibitors of each of the PDE families are listed in Table I; well-known nonselective inhibitors include caffeine, theophylline, pentoxifylline, and 3-isobutyl-1-methylxanthine.¹³ Although type-selective inhibitors offer the potential for specificity of pharmacologic effect, the structural similarities and apparent functional redundancy within subtypes and isoforms have renewed concerns for the identification and utility of more highly selective agents.^{20,21} Nevertheless, the recent reports of decreased bronchial hyperresponsiveness in PDE4D knockout mice has re-energized the field of PDE research for atopic diseases.²²

PDEs are composed of 3 broad functional domains: a regulatory N-terminus, a central catalytic domain, and a regulatory C-terminus.²³ The catalytic domains are highly homologous across families (>50% sequence identity at the amino acid level). The N-terminal and C-terminal domains display moderate homology within families and impart to specific subtypes and isoforms their unique functional fingerprints. The N-terminus is involved in allosteric regulation (calmodulin, cyclic nucleotide, and metal ion binding; phosphorylation sites) and membrane targeting.²⁴⁻³⁰ Recent data suggest that the C-terminus may be involved in dimerization and possess docking sites for PDE-specific kinases.^{24,31}

PHARMACOLOGY

The general schema for the formation and degradation of cyclic nucleotides is depicted in Fig 1. Cyclic AMP and guanosine 3', 5'-cyclic monophosphate (cGMP) are formed from their respective triphosphates by the catalytic activity of adenylyl cyclase (AC) or guanylyl cyclase (GC), respectively. These cyclases exist in multiple isoforms (9 for AC; 11 for GC). Each isoform has a specific tissue and cellular distribution, and each couples specifically to discrete sets of receptors for signal transduction.³² Some isoforms are regulated by transactivators such as calmodulin, whereas others are sensitive to phosphorylation.³³ Thus, adenylyl and guanylyl cyclase are able to integrate a vast array of direct and cross-talk signals and to do so differently in different cell types.

Cyclic nucleotides are degraded by PDE-catalyzed hydrolytic cleavage of the 3'-phosphodiester bond, resulting in formation of the corresponding inactive 5'-monophosphate. PDE inhibitors block this hydrolytic activity, causing accumulation of cyclic nucleotides corresponding to the type-specificity of the inhibitor used (eg, accumulation of cAMP when inhibiting a cAMP-specific PDE such as PDE4). Interestingly, activation of AC or GC fails to induce more than transient alterations in cyclic nucleotides because of compensatory increases in PDE activity; however, concomitant cyclase activation and PDE inhibition produce synergistic effects on cyclic nucleotide steady-state levels.^{34,35}

Specific PDE isoforms display remarkably selective cellular and subcellular localizations.^{18,36,37} Thus, compartmentalization of PDE activities possessing discrete pharmacokinetic and regulatory characteristics likely plays an important role in the maintenance of cellular homeostasis. This type of compartmentalization may also contribute to rapid and reversible cross-talk between PDE families and isoforms; a local shift in cyclic nucleotide content within one of these subcellular pools through the activity of one PDE might affect allosteric regulation or active site competition on another PDE.^{38,39} Clearly, pharmacologic regulation of PDEs must account for a complex set of variables.

Cyclic nucleotides transduce signals through direct protein binding. The best characterized of these protein targets are the cyclic nucleotide-dependent protein kinases, cAK and cGK. Each is composed of 2 major subtypes (cAKI and cAKII; cGKI and cGKII); each subtype is composed of several isoforms.^{40,41} Cyclic AK and cGK are serine-threonine kinases, each a tetramer of 2 regulatory subunits coupled to 2 catalytic subunits. When activated through cooperative binding of 4 cyclic nucleotide molecules, the 2 regulatory domains disengage from the 2 catalytic domains. These catalytic domains are then free to translocate within the cell and phosphorylate specific targets including transcription regulators, ion channels, and signaling proteins.⁴²⁻⁴⁵ This translocation is not a random process. In the case of cAK, subcellular targeting is enhanced by the family of A kinase anchor proteins (AKAPs, at least 20 isoforms, each differentially regulated and expressed in specific tissues). AKAPs' hydrophobic docking sites bind the catalytic subunits of cAK, and their coiled coil regions interact with various structural or functional proteins to complete the targeting process.⁴⁶⁻⁵⁰ Interestingly, targets for regulation by cAK and cGK include AC and GC, several AKAPs, and several PDEs. Thus, multiple levels of degeneracy, cross-talk, and feedback create a cyclic nucleotide-mediated signaling network of extreme complexity.

Two final points concerning cyclic nucleotide signaling should be underscored. First, the cyclic nucleotide signaling cascade engages in cross-talk with several other critical signaling pathways. For example, cAK targets Raf-1 in the RAS/mitogen-activated protein kinase pathway, whereas Erk2 kinase targets several isoforms of PDE4.²¹ Moreover, several pathways may independently

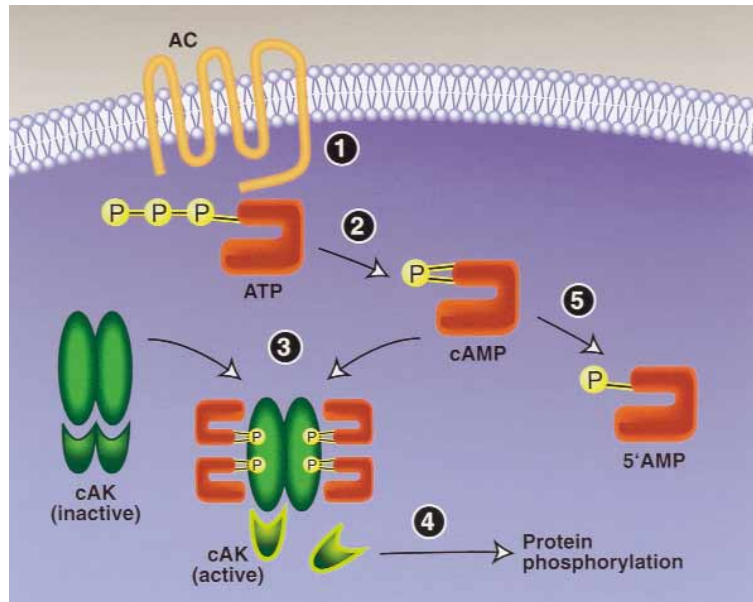


FIG 1. Cyclic nucleotide signaling and homeostasis. Activation of ACs (1) results in the generation of cAMP from adenosine triphosphate (ATP; 2). Four molecules of cAMP cooperatively bind to the 2 regulatory subunits of inactive cAK (3), resulting in disengagement of 2 active catalytic subunits that are capable of protein phosphorylation (4). The hydrolysis of cAMP to inactive 5'-adenosine monophosphate (5'AMP) is catalyzed by various cAMP-specific PDEs (5).

TABLE I. Human cyclic nucleotide phosphodiesterase isozymes

Family (no. of genes)	Characteristics	K_m ($\mu\text{mol/L}$): cAMP; cGMP	Primary tissue distribution	Examples of inhibitors
PDE1 (3)	Ca^{2+} /calmodulin-stimulated	1-30; 3	Heart, brain, lung, smooth muscle	KS-505a Vinpocetine
PDE2 (1)	cGMP-stimulated	50; 50	Adrenal gland, heart, lung, liver, platelets	EHNA (MEP-1)
PDE3 (2)	cGMP-inhibited, cAMP-selective	0.2; 0.3	Heart, lung, liver, platelets, adipose tissue, immunocytes	Cilostamide Enoxamone Milrinone Siguzodan
PDE4 (4)	cAMP-specific, cGMP-insensitive	4; >3000	Sertoli cells, kidney, brain, liver, lung, immunocytes	CDP840 Rolipram SB 207499 Tibenelast
PDE5 (1)	cGMP-specific	150; 1	Lung, platelets, smooth muscle	Dipyridamole MY-5445 Sildenafil Zaprinast
PDE6 (3)	cGMP-specific	2000; 60	Photoreceptors	Dipyridamole Zaprinast
PDE7 (2)	cAMP-specific, high-affinity	0.2; >1000	Skeletal muscle, heart, kidney, brain, pancreas, T lymphocytes	Several in development
PDE8 (2)	cAMP-selective, IBMX insensitive	0.06; N/A	Testes, eye, liver, skeletal muscle, heart, kidney, ovary, brain, T lymphocytes	None selective
PDE9 (1)	cGMP-specific, IBMX insensitive	N/A; 0.17	Kidney, liver, lung, brain	None selective
PDE10 (1)	cGMP-sensitive, cAMP-selective	0.05; 3.0	Testes, brain	None selective
PDE11 (1)	cGMP-sensitive, dual specificity	0.7; 0.5	Skeletal muscle, prostate, kidney, liver, pituitary and salivary glands, testes	None selective

IBMX, 3-isobutyl-1-methylxanthine.

regulate cyclic nucleotide downstream effectors (a process called *convergence*). For example, both cAK and the immunoglobulin Fc signaling cascades target the transcription factor CREB at different sites on the molecule and exert different effects.^{51,52} The outcome of cross

talk or convergence may be either inhibition or enhancement of signaling. Second, the cyclic nucleotide pathway undergoes autoregulation. For example, transcription of several PDE genes are under the control of cyclic nucleotide regulatory elements, and several PDE proteins

TABLE II. cAMP-PDE expression and significance in human inflammatory/accessory cells

Basophils	PDE3, PDE4, PDE5	Decreased histamine release Decreased IL-4 and IL-13 generation Decreased LTC4 generation
B lymphocytes	PDE3, PDE4, PDE7	Decreased IgE synthesis Increased proliferation
Dendritic cells	PDE3, PDE4, PDE5	Decreased cytokine generation Decreased T-cell help
Endothelial cells	PDE1, PDE2, PDE3, PDE4, PDE5, PDE7	Decreased calcium fluxes Decreased cytokine generation Decreased hyperpermeability Decreased VCAM-1 and L-selectin expression
Eosinophils	PDE4, PDE3	Decreased CD11b/CD18 expression Decreased chemotaxis Decreased degranulation Decreased L-selectin shedding Decreased LTC4 generation Decreased superoxide generation Decreased survival
Macrophages	PDE1, PDE3, PDE4 PDE5	Decreased arachidonic acid release Decreased TNF- α , IL-1 β , and IL-10 generation
Mast cells	PDE3, PDE4	Decreased cytokine generation Decreased histamine release
Monocytes	PDE3, PDE4	Decreased arachidonic acid release Decreased leukotriene generation Decreased TNF- α generation No effect on IL-1 β , IL-6, IL-8 No effect on superoxide or nitric oxide generation
Neutrophils	PDE4	Increased IL-10 generation Decreased apoptosis Decreased calcium signaling Decreased CD11b expression Decreased degranulation Decreased elastase secretion Decreased IL-8 secretion Decreased leukotriene generation Decreased superoxide generation
T lymphocytes	PDE1, PDE2, PDE3, PDE4, PDE5, PDE7, PDE8	Decreased adhesion molecule expression Decreased blastogenesis Decreased proliferative response Decreased cytokine generation (IL-2, IL-4, IL-5, IL-13, IFN- γ , TNF, GM-CSF) Increased IL-10 generation

have cAK and/or cGK phosphorylation sites.^{53,54} The outcome of autoregulation may be either positive or negative feedback.

IN VITRO EFFECTS

Inflammatory cells are exquisitely sensitive to alterations in cyclic nucleotide levels; interestingly, modulation of immune cell function by selective PDE inhibitors is limited to specific PDE types, probably as a result of compartmentalization of cyclic nucleotide and PDE pools. In immune cells, elevation of intracellular cAMP, mediated predominantly through inhibition of PDE4, results in a wide range of anti-inflammatory effects, as summarized in Table II.

Basophils and mast cells

Human basophils contain primarily PDE3, PDE4, and PDE5. Inhibition of PDE4 has been shown to downregulate anti-IgE-induced histamine release and leukotriene C4 (LTC4) generation, platelet-activating factor-induced histamine release, and dust mite antigen-induced IL-4 and IL-13 generation from human basophils.⁵⁵⁻⁵⁹ Although PDE3 and PDE5 inhibitors show little independent efficacy in regulating these functions, PDE3 inhibitors may potentiate the activity of PDE4 inhibitors on several of these activities.^{56,57,59} Finally, functional immunomodulation is closely correlated with intracellular cAMP levels; synergy is observed with PDE4 inhibitors and forskolin.⁵⁸ To date, there are no studies probing the potential utility of inhibitors targeting PDE7-PDE11.

Human mast cells contain both PDE3 and PDE4. Interestingly, although some investigators have reported that PDE4 inhibitors downregulate IgE-mediated calcium fluxes, histamine release, and cytokine generation, several groups have reported resistance of mast cell mediator release to PDE4 inhibition and have correlated this resistance with a lack of PDE4-mediated increases in intracellular cAMP.^{58,60-63} Differences in cellular substrate for these studies (skin and lung fragments vs purified mast cells vs cultured mast cells) may account for some of these discrepancies. This remains an area of unresolved debate.

Eosinophils

Human eosinophils contain both PDE3 and PDE4.⁶⁴ PDE4 inhibitors block a variety of eosinophil functions, including superoxide generation, LTC₄ production, CD11b/CD18 upregulation and L-selectin shedding, chemotaxis, and survival; inhibitors of PDE3 show no independent efficacy in downregulating eosinophil functions.⁶⁵⁻⁷¹ Several recent reports suggest both synergy between AC activators and PDE4 inhibitors in downregulating various eosinophil functions and reversal of the effects of PDE4 inhibitors on freshly isolated human eosinophils by cAK antagonists.^{35,71} The effects of PDE4 inhibitors on eosinophil-derived cytokine generation and the potential roles of PDE7-PDE11 have not been reported.

Lymphocytes

B lymphocytes contain PDE3, PDE4, and PDE7.⁷² Several authors have described complex relationships between intracellular cAMP, IL-4, and IgE synthesis. Unfortunately, these studies have been performed in mixed cell populations in which the concomitant effects of T cells and accessory cells are not adequately controlled.⁷³⁻⁷⁵ However, even studies with purified B cells have yielded seemingly contradictory results. Whereas proliferation of polyclonally stimulated, purified B lymphocytes is enhanced by PDE4 inhibitors, cAK activation results in inhibition of B-cell receptor-mediated proliferation and enhanced apoptosis that is subject to rescue by IL-4.^{72,76} Finally, although PDE4 inhibitors have been shown to reduce spontaneous IgE release from mononuclear cells isolated from allergic subjects, these effects have not been observed with purified B cells.^{77,78} The effects of PDE inhibition on synthesis of other immunoglobulin classes, B-cell differentiation, and cytokine generation have not been reported. This is an area with great research potential.

In addition to PDE3, PDE4, and PDE7, T lymphocytes express PDE1, PDE2, PDE5, and PDE8. The distribution of PDE types is nearly identical in CD4⁺ and CD8⁺ lymphocytes, but subtype and isoform expression may vary among T-cell phenotypes and in disease states.^{64,79-81} In general, PDE4 inhibitors downregulate mitogen-, antigen-, and allogeneic HLA class II-induced blastogenesis and T-cell proliferation. Although PDE3 inhibitors show little or no independent efficacy in these models, they do synergize with the PDE4 inhibitors. PDE5 inhibitors are ineffective.^{80,82-84} PDE4 inhibitors also downregulate mitogen- or antigen-induced production of many T_H1- and

T_H2-derived proinflammatory cytokines, including IL-2, IL-4, IL-5, IL-13, IFN- γ , TNF, and GM-CSF; interestingly, upregulation of IL-10 has also been reported.^{79,80,85,86} Once again, although PDE3 inhibitors show no independent efficacy in these models, they do synergize with PDE4 inhibitors. More recently, PDE4 inhibitors were shown to downregulate adhesion molecule expression on T cells and promote neoantigen tolerance in murine T cells.⁸⁷⁻⁸⁹ Finally, inhibition of PDE7 through use of antisense technology has demonstrated efficacy in downregulating anti-CD3- anti-CD-28-mediated proliferation and IL-2 production.⁹⁰ The functional role of PDE8-PDE11 in T lymphocytes has not been pursued.

Monocytes/macrophages/dendritic cells

Human monocytes contain PDE3 and PDE4; macrophages retain PDE4 and upregulate PDE3 while gaining PDE1 and PDE5; dendritic cells downregulate PDE4, upregulate PDE3, and gain only PDE5.^{64,91,92} These data underscore the importance of PDEs in the differentiation and maintenance of immunologic phenotypes. Inhibition of PDE4 markedly downregulates TNF- α production and arachidonic acid release/LT generation from monocytes.^{55,93,94} Interestingly, PDE4 inhibitors do not modulate superoxide, nitric oxide, IL-6, or IL-8 production from human monocytes.⁹⁵⁻⁹⁷ Although the data concerning PDE4 inhibitor effects on IL-1 β production from monocytes are conflicting, PDE4 inhibitors consistently upregulate IL-10 production from these cells.^{86,98,99} Inhibition of PDE4 in macrophages is associated with weak downregulation of TNF- α and IL-1 β production and arachidonic acid release.⁹⁹⁻¹⁰¹ Interestingly, whereas PDE3 inhibitors display only minimal independent efficacy and variable synergy with PDE4 inhibitors in monocytes, inhibition of PDE3 in macrophages is associated with significant independent suppression of TNF- α production, nitric oxide generation, and IL-10 secretion.^{99,102,103} These differences between monocytes and macrophages may be attributable, in part, to maturation-induced changes in PDE profile. PDE4 inhibitors also downregulate T-cell help and cytokine generation from dendritic cells; although PDE3 inhibitors show marginal independent efficacy in dendritic cells, they show marked synergy with PDE4 inhibitors.^{67,92} The effects of PDE inhibitors on adhesion molecule expression and antigen presentation have not been reported; the potential roles of PDE1, PDE5, and PDE7 through PDE11 have not been explored.

Neutrophils

Neutrophils contain predominantly PDE4. Inhibitors of PDE4 enhance intracellular calcium resequestration and decrease degranulation, superoxide and LT production, elastase and IL-8 secretion, and CD11b surface expression.^{55,65,104-106} Interestingly, PDE4 inhibitors also antagonize proapoptotic signals in neutrophils.¹⁰⁷ Whereas PDE3 and PDE5 inhibitors show little or no efficacy in modulating these cellular functions, AC inducers act in an additive or synergistic fashion with PDE4 inhibitors in

downregulating most neutrophil cellular functions.^{105,106,108} The potential roles of PDEs other than PDE3, PDE4, and PDE5 have not been explored.

Endothelial cells

Endothelial cells contain predominantly PDE2, PDE3, and PDE4, with lesser contribution of PDE1, PDE5, and PDE7.¹⁰⁹⁻¹¹¹ Whereas PDE4 inhibitors decrease calcium fluxes and growth factor secretion, PDE3 inhibitors decrease monocyte chemoattractant protein 1, and the combination of PDE3 and PDE4 inhibitors downregulates hyperpermeability, VCAM-1 expression, and E-selectin expression (but not ICAM-1 expression).^{109,112-115}

IN VIVO EFFECTS

PDE inhibitors have been evaluated as potential antipressants, anti-inflammatory agents, antiproliferative agents, antihypertensive and cardiovascular agents, and cytoprotective agents.^{13,116-120} To date, clinical development of selective PDE inhibitors has focused primarily on PDE3, PDE4, and PDE5. Despite early promise, clinical development of PDE3 inhibitors for congestive heart failure was essentially abandoned because of a concomitant increase in the incidence of cardiac arrhythmias; interest in the role of PDE3 in adipocyte metabolism remains.^{121,122} Although their postulated cardiovascular utility was not realized, a PDE5 inhibitor has been marketed for the treatment of male sexual dysfunction; interestingly, the neuroophthalmologic side effects of sildenafil may be attributed to cross-reactivity on photoreceptor PDE6 and not to the trace presence of PDE5 in the eye.^{123,124} The only currently available PDE inhibitors for the treatment of immune/inflammatory diseases are the nonselective xanthine derivatives (aminophylline, theophylline, etc); these have been reviewed elsewhere.^{125,126} Although PDE1, PDE3, and PDE5 inhibitors show little or no independent efficacy for this indication, PDE4 inhibitors have demonstrated activity in inhibiting antigen-induced bronchoconstriction and airway hyperresponsiveness, antigen-induced eosinophil infiltration, and local cytokine generation in a variety of preclinical models for pulmonary allergic inflammation.¹²⁷⁻¹³⁰ Unfortunately, clinical trials with PDE4 inhibitors have demonstrated dose-limiting toxicity due to gastric hypersecretion and emesis; this toxicity is poorly reproduced in rodents and nonhuman primates but is modeled well in ferrets.¹³¹

Published results of clinical trials with selective PDE inhibitors remain quite limited. Several combined PDE3/PDE4 inhibitors (benzafentrine, zardaverine) have been administered; however, efficacy endpoints focused primarily on bronchodilatation. The results of these studies have ranged from negative to mildly effective (roughly equivalent to that of a β_2 -agonist). Anti-inflammatory endpoints were not sought in these studies, the studies were not clearly of sufficient duration to evaluate an anti-inflammatory endpoint, and adverse events characteristic of PDE3 inhibitors limited the utility of these agents.^{132,133} Tibenalast, a weak first-generation PDE4 inhibitor, was

only minimally effective in improving pulmonary function in a cohort of 40 asthmatic subjects treated in a double-blinded, placebo-controlled crossover study; however, a minimal adverse event profile in these subjects suggested little evidence of systemic PDE4 inhibition, and the dosing regimen and duration of the study precluded assessment of anti-inflammatory contributions to clinical efficacy.¹³⁴ CP80,633, a moderate-strength first-generation PDE4 inhibitor, was evaluated for topical use in 20 subjects with atopic dermatitis. When used on symmetrically involved disease sites over a 28-day period in a double-blinded and paired comparison, CP80,633 induced clinical improvement in 20 of 20 subjects; the topical route of administration obviated systemic toxicity.¹³⁵

More recent advances in our understanding of the molecular pharmacology of PDE4 isozymes has led to the development of second-generation PDE4 inhibitors that preserve the anti-inflammatory efficacy of these agents while reducing the incidence of emesis.^{55,136} Several of these second-generation PDE4 inhibitors are in clinical trials. Administration of CDP840 orally in a double-blinded, placebo-controlled trial was associated with significant ablation of the asthmatic late-phase response after allergen challenge without significantly altering the immediate response to histamine challenge. These data suggest an anti-inflammatory mechanism of action; dose-limiting toxicity was not seen in this study.¹³⁷ Oral administration of SB207499 (cilomilast, Ariflo) to a population of pure asthmatics in a double-blinded, placebo-controlled study was associated with clinically relevant and sustained improvements in pulmonary function parameters; once again, the product was well tolerated.¹³⁸ Development of cilomilast continues for the treatment of chronic obstructive pulmonary disease.^{139,140} Finally, administration of roflumilast significantly inhibited the late-phase asthmatic response to antigen challenge and significantly reduced the fall in lung function associated with exercise challenge in exercise-induced asthma; this product was also well tolerated.^{141,142} Several additional second-generation PDE4 inhibitors are in preclinical and early-stage clinical development.

CONCLUSIONS

The past several years have witnessed significant advances in our understanding of the molecular pharmacology of cyclic nucleotide PDEs. With the advent of second-generation PDE4 inhibitors, the continued success of PDE5 inhibitors, and recent advances in rational structure/function drug design, the therapeutic promise of selective PDE inhibitors may soon be realized.

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