

Advances in targeting cyclic nucleotide phosphodiesterases

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Abstract | Cyclic nucleotide phosphodiesterases (PDEs) catalyse the hydrolysis of cyclic AMP and cyclic GMP, thereby regulating the intracellular concentrations of these cyclic nucleotides, their signalling pathways and, consequently, myriad biological responses in health and disease. Currently, a small number of PDE inhibitors are used clinically for treating the pathophysiological dysregulation of cyclic nucleotide signalling in several disorders, including erectile dysfunction, pulmonary hypertension, acute refractory cardiac failure, intermittent claudication and chronic obstructive pulmonary disease. However, pharmaceutical interest in PDEs has been reignited by the increasing understanding of the roles of individual PDEs in regulating the subcellular compartmentalization of specific cyclic nucleotide signalling pathways, by the structure-based design of novel specific inhibitors, and by the development of more sophisticated strategies to target individual PDE variants.

Efficient integration of myriad extracellular and intracellular signals is required to maintain adaptive cellular functioning. Dysregulation of this integration promotes maladaptive cellular functions and underpins human diseases. Numerous distinct cellular signal transduction systems have evolved to allow cells to receive these various inputs, to translate their codes and, subsequently, to transduce and integrate their meanings. Two of these, the cAMP and the cGMP signalling systems (sometimes together referred to as the cyclic nucleotide signalling system), are among the earliest identified signal transduction systems. Advances in our understanding of the mechanisms by which cellular functions are altered through cyclic nucleotide signalling are enabling the identification and development of therapeutic agents for use in numerous human diseases.

The cAMP- and cGMP-signalling systems regulate a vast number of physiological processes, including visual transduction, cell proliferation and differentiation, gene expression, inflammation, apoptosis and metabolic pathways such as steroidogenesis, insulin secretion and glycogen synthesis, as well as glycometabolysis, lipogenesis and lipolysis^{1–3}. Once synthesized by adenylyl cyclases or guanylyl cyclases, respectively, cAMP and cGMP transduce signal-encoded information by acting through a number of cellular effectors. These include cAMP- or cGMP-activated protein kinases (protein kinase A (PKA) or PKG, respectively), cyclic nucleotide-gated ion channels,

a family of two cAMP-activated guanine nucleotide exchange proteins (exchange factors directly activated by cAMP 1 (EPAC1) and EPAC2) and a limited group of enzymes from the cyclic nucleotide phosphodiesterase (PDE) family, which contain allosteric cyclic nucleotide-binding sites in addition to their catalytic sites^{4–6}. Because the activities of several of these effectors can be altered simultaneously in response to increases in cellular cAMP or cGMP, cyclic nucleotide-elevating agents can trigger multiple cellular signalling events that — when integrated — yield a variety of finely-tuned ‘read-outs’ and that markedly affect the numerous cellular functions listed above.

The functional impact and therapeutic utility of agents that increase the synthesis of either cAMP or cGMP have been established^{7–10}. Indeed, agents that are designed to act by binding to and activating selected G protein-coupled receptors (GPCRs), including drugs such as salmeterol (for asthma)¹¹ or exenatide-4 (for diabetes)¹², affect cellular functions by stimulating adenylyl cyclases. Similarly, agents that promote guanylyl cyclase-catalysed synthesis of cGMP have therapeutic utility; these include nitric oxide donor drugs such as glyceryl trinitrate (for angina therapy)¹³ or the natriuretic peptide-inspired drugs¹⁴ such as nesiritide, a recombinant form of human B-type natriuretic peptide (BNP).

The functional impact and therapeutic utility of blocking cyclic nucleotide hydrolysis catalysed by cyclic nucleotide PDEs have also long been recognized. Indeed,

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Physiology And Pharmacology Of Cyclic Amp Advances In Cyclic Nucleotide Research Volume 1

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Second International Conference on Cyclic AMP, Vancouver, British Columbia, Canada, July 8-11, 1974 George I. Drummond,Paul Greengard,G. Alan Robison,1975 *The Chemistry and Pharmacology of Prostaglandins* Norman Kharasch,1972 *Advances in Cyclic Nucleotide Research* Paul Greengard,G. Alan Robison,1975 *Journal of Cyclic Nucleotide Research* ,1975 *Thrombosis Et Diathesis Haemorrhagica* ,1975 **Library of Congress Catalog** Library of Congress,1973 Beginning with 1953 entries for Motion pictures and filmstrips Music and phonorecords form separate parts of the Library of Congress catalogue Entries for Maps and atlases were issued separately 1953 1955 Intra-science Chemistry Reports ,1972 **Library of Congress Catalogs** Library of Congress,1976 *Search* ,1974 **Advances in Cyclic Nucleotide and Protein Phosphorylation Research** ,1984 **Journal of Chromatography** ,1973 *Canadian Journal of Physiology and Pharmacology* ,1979 Medical Books and Serials in Print R. R. Bowker LLC,R.R. Bowker Company,1978 *The Publishers' Trade List Annual* ,1978 *Bibliography of Column Chromatography, 1967-1970 and Survey of Applications* Zdeněk Deyl,1973 *Journal of Scientific & Industrial Research* ,1976 **National Union Catalog** ,1978 Includes entries for maps and atlases

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