

Phosphodiesterases

Key References

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Overview

Cyclic nucleotide phosphodiesterases (PDEs) catalyze the hydrolysis of cAMP and/or cGMP. They function with adenylyl and guanylyl cyclases to regulate the amplitude and duration of responses triggered by the second messengers, cAMP and cGMP. In doing so they regulate a wide range of biological responses triggered by light, hormones, neurotransmitters and odorants. Two classes of functional PDEs, which do not share any sequence homology, are recognized: Class I PDEs, found in all eukaryotic cells and Class II PDEs, found in lower eukaryotes.

There are 11 different mammalian PDE families of which PDE4, PDE7 and PDE8 are specific for cAMP, while PDE5, PDE6 and PDE9 are specific for cGMP and others hydrolyze both cAMP and cGMP. However, PDE3 whose V_{\max} cAMP > V_{\max} cGMP and K_m cGMP < K_m cAMP is generally considered as a cGMP-inhibited cAMP hydrolyzing PDE.

PDEs contain a conserved, catalytic domain of around 250 amino acids, where an invariant glutamine provides the key specificity determinant by scanning the purine moiety in cAMP/cGMP. Adjacent residues anchor this glutamine in different orientations so as to define specificity for either or both cAMP/cGMP.

Twenty-one genes encode the 11 known PDE families with additional isoform diversity generated through alternative mRNA splicing and the use of distinct promoters. Isoforms have an extreme N-terminal domain that uniquely characterizes them. In various PDE families, and particularly with PDE4, this is involved in intracellular targeting. Different cell types express a unique complement of PDE isoforms,

thereby individually tailoring the nature of the spatial and kinetic characteristics of the cAMP signal. This defines the characteristics of compartmentalized cAMP signaling operating in such cells.

For various PDEs, located immediately N-terminal to the catalytic unit are family-specific paired regulatory domains. These allow regulation through cross-talk with various other signal transduction systems by either phosphorylation or allosteric regulation.

PDEs are named to identify isoforms. Thus, HSPDE4A1 refers to the Homo sapiens PDE4 family, gene A, splice variant 1. The high level of sequence conservation among species, distinct intracellular targeting and kinetic and regulatory characteristics suggest that individual PDEs play particular roles in specific physiological processes. For example, PDE1 isoforms have twin regulatory domains that allow them to bind and be activated by Ca^{2+} /calmodulin, providing cross talk between the Ca^{2+} and cAMP/cGMP signaling pathways. They can participate in the feed-forward amplification of neuronal signals. PDE2 has twin regulatory GAF domains that allow binding and activation by cGMP, providing cross talk with the cGMP/NO signaling pathway. Indeed, PDE2A plays a role in regulating aldosterone production in adrenal glomerulosa cells through integration of cAMP and cGMP signals. PDE3, which hydrolyses cAMP, has a unique insert in its catalytic region, which attenuates its cGMP hydrolysing capacity such that cGMP potently inhibits cAMP hydrolysis by this enzyme. This allows elevation of cGMP to potentiate cAMP signals, which has functional significance in regulation of platelet aggregation. PDE3B underpins the anti-lipolytic action of insulin in adipocytes through being phos-

phorylated and activated by PKB/Akt. PDE3, together with PDE4 isoforms, provide the major cAMP hydrolyzing activity in many cells. PDE4 isoforms underpin much of compartmentalized cAMP signaling by interacting with a range of scaffold proteins, including β arrestin, AKAPs, SRC kinases, myomegalin and RACK1. Their phosphorylation by ERK configures cross-talk with this pathway and phosphorylation by PKA promotes cAMP desensitization. Chemical and genetic knockout identifies PDE4s as having a key role in inflammatory responses, memory and depression. PDE5, has cGMP-binding, regulatory GAF domains and plays a role in regulating smooth muscle tension in certain vascular beds. Sildenafil, a selective PDE5A inhibitor, is used to treat erectile dysfunction. PDE6 plays a central role in visual phototransduction through rapid modulation of cGMP hydrolysis subsequent to activation by GTP-bound transducin. The functional significance of the newer PDEs is not well appreciated and they provide a challenge for the future in understanding their physiological roles.

Phosphodiesterases

| FAMILY NAME | PDE1 | PDE2 | PDE3 | PDE4 | PDE5 | PDE6 |
|--|---|--|--|--|--|---|
| KNOWN GENES ^a | 1A, 1B, 1C | 2A | 3A, 3B | 4A, 4B, 4C, 4D | 5A | 6A, 6B |
| DESCRIPTIVE NAME | CaM-dependent PDE | cGMP-stimulated PDE | cGMP-inhibited PDE | cAMP-specific PDE | cGMP-binding PDE | Photoreceptor PDE |
| STRUCTURAL INFORMATION ^b | 535 aa (human) HSPDE1A3 | 941 aa (human) HSPDE2A3 | 1141 aa (human) HSPDE3A1 | 647 aa (human) HSPDE4A1 | 874 aa (human) HSPDE5A1 | 860 aa (human) HSPDE6A1 |
| REGULATORS | Ca ²⁺ /CaM (21272) | cGMP (G6129) | cGMP (G6129) Insulin (I5500 (b), I0259 (h)) Leptin (L4146 (h), L3772 (m), L5037 (r)) | PKA (P5511) ERK phosphatidic acid | PKG | Light |
| SUBSTRATE SPECIFICITY | cAMP (A6885) or cGMP (G6129) | cAMP (A6885) or cGMP (G6129) | cAMP (A6885) or cGMP (G6129) | cAMP (A6885) | cGMP (G6129) | cGMP (G6129) |
| INHIBITORS ^c | Vinpocetine (V6383) ^d SCH-51866 ^d | *EHNA (E114) *BAY60-7550 | *Cilostamide Enoximone (E1279) Imazodan (I0782) Trequinsin (T2057) Milrinone (M4659) | *Rolipram (R6520) *Ro 20-1724 (B8279) *RP73401 | *Sildenafil *Vardenafil Dipyridamole (D9766) ^d T-1032 (T7692) Zaprinast (Z0878) ^d | Zaprinast (Z0878) ^d Dipyridamole (D9766) ^d |
| MAJOR TISSUE EXPRESSION | Brain, heart, smooth muscle, olfactory cilia | Adrenal cortex, brain, heart | Heart, adipose, pancreas, platelets | Many tissues | Lung, platelets, smooth muscle, corpus collusum | Rod and cone photoreceptor outer segments |
| PHYSIOLOGICAL FUNCTION | Sperm development and maturation (?), monocyte/macrophage differentiation (?), olfactory neuron regulation (?), neuronal regulation (?) | β2/β3 regulation of cardiac myocytes, endothelial cell function | Platelet function, adipocyte function | Regulates monocyte, macrophage, T-cell, eosinophil, neutrophil function; regulates neuronal function and differentiation; regulates functions of inflammatory cells and vascular smooth muscle cells; pro- apoptotic; anti-apoptotic; endothelial cell function; inhibition of bone loss | Vascular smooth muscle cell relaxation | Visual signal transduction |
| DISEASE RELEVANCE | Fertility, inflammation, olfaction | Heart disease, anti-angiogenic | Intermittent claudication peripheral arterial occlusive disease, restenosis, obesity, type-2 diabetes | Airway inflammation (asthma, COPD), rheumatoid arthritis, Crohn's disease, learning, memory, schizophrenia, spinal cord injury, stroke, restenosis, chronic B-cell lymphocytic leukemia, spinal cord injury, Parkinson's Disease, anti- angiogenic, osteopenia including osteoporosis | Penile erectile dysfunction, pulmonary hypertension, migraine | Retinopathies |

Phosphodiesterases

| FAMILY NAME | PDE7 | PDE8 | PDE9 | PDE10 | PDE11 |
|-------------------------------------|---------------------------------|--|---------------------------------|---|---|
| KNOWN GENES ^a | 7A, 7B | 8A, 8B | 9A | 10A | 11A |
| DESCRIPTIVE NAME | High affinity cAMP-specific PDE | cAMP-specific PDE | High affinity cGMP-specific PDE | Dual specificity PDE | Dual specificity PDE |
| STRUCTURAL INFORMATION ^b | 482 aa (human) HSPDE7A1 | 713 aa (human) HSPDE8A1 | 593 aa (human) HSPDE9A1 | 779 aa (human) HSDPE10A1 | 490 aa (human) HSPDE11A1 |
| REGULATORS | Not known | Not known | Not known | PKA (P5511) | Not known |
| SUBSTRATE SPECIFICITY | cAMP (A6885) | cAMP (A6885) | cGMP (G6129) | cAMP (A6885) or cGMP (G6129) | cAMP (A6885) or cGMP (G6129) |
| INHIBITORS ^c | BRL50481 | Dipyridamole (D9766) ^d | SCH-51866 ^d | SCH-51866 ^d Zaprinast (Z0878) ^d Dipyridamole (D9766) ^d | Zaprinast (Z0878) ^d Dipyridamole (D9766) ^d |
| MAJOR TISSUE EXPRESSION | Skeletal muscle, T-cells | Testis, liver, thyroid | Kidney | Testis, brain | Skeletal muscle, prostate |
| PHYSIOLOGICAL FUNCTION | Not known | Thyroid function (?), osteoblast function (?), T-cell activation (?), sperm function (?) | Not known | Striatal neuron function | Sperm function (motility, number) |
| DISEASE RELEVANCE | | Hyperthyroidism, metabolic bone disease | Fertility | Parkinsonism, schizophrenia, obsessive compulsive disorders, addictions | Fertility |

Abbreviations

CaM: Calmodulin

EHNA: Erythro-9-(2-hydroxy-3-nonyl)adenine

PKA: cAMP-dependent protein kinase

PKG: cGMP-dependent protein kinase

Ro 20-1724: 4-[(3-Butoxy-4-methoxyphenyl)methyl]2-imidazolidinone

RP 73401: N-(3,5-Dichloropyrid-4-yl)-3-cyclopentyl-4-methoxybenzamide

SB-207499: c-4-Cyano-4-(3-cyclopentyl-4-methoxyphenyl)-r-1-cyclohexane carboxylic acid

SCH-51866: cis-5,6a,7,8,9,9a-Heptahydro-2-[4-(trifluoromethyl)phenylmethyl]-5-methyl-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one

T-1032: Methyl-2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-3-isoquinoline carboxylate sulfate

b: bovine

h: human

m: mouse

r: rat

FOOTNOTES

a Multiple splice variants exist for most of these enzymes. See reviews for a more complete listing and nomenclature.

b One particular splice variant is listed from each PDE family. HS = Homo sapiens.

c Sever

pentoxyfylline (**P1784**) and 1,3-dipropyl-7-methylxanthine (**D108**).

d Selective inhibitors for the PDE1, PDE6, PDE7, PDE8, PDE9, PDE10 and PDE11 families are not currently available. Similarly, the compounds zaprinast and dipyridamole, once thought to be reasonably selective for the PDE5 and PDE6 families, are now known to also inhibit the PDE8, PDE10 and PDE11 families.

*Specific inhibitors that achieve reversible chemical inhibition of this particular family.

(**IBMX I5879**), theophylline (**T1633**), papaverine (**P3510**),