

Cyclic Nucleotide Phosphodiesterases

Key References

- Beavo, J.A. et al. "Multiple cyclic nucleotide phosphodiesterases." *Mol. Pharmacol.* **46**, 399-405 (1994).
- Conti, M., Jin, S.L.C. "The molecular biology of cyclic nucleotide phosphodiesterases." *Prog. Nucleic Acid Res. Mol. Biol.* **63**, 1-38 (2000).
- Dousa, T.P. "Cyclic-3',5'-nucleotide phosphodiesterase isozymes in cell biology and pathophysiology of the kidney." *Kidney Int.* **55**, 29-62 (1999).
- Juilfs, D.M. et al. "A subset of olfactory neurons that selectively express cGMP-stimulated phosphodiesterase (PDE2) and guanylyl cyclase-D define a unique olfactory signal transduction pathway." *Proc. Natl. Acad. Sci. USA* **94**, 3388-3395 (1997).
- Li, L. et al. "CD3- and CD28-dependent induction of PDE7 required for T cell activation." *Science* **283**, 848-851 (1999).
- Manganiello, V.C., Degerman, E. "Cyclic nucleotide phosphodiesterases: Diverse regulators of cyclic nucleotide signals and inviting molecular targets for novel therapeutic agents." *Thromb. Haemost.* **82**, 407-411 (1999).
- Soderling, S.H., Beavo, J.A. "Regulation of cAMP and cGMP signaling: New phosphodiesterases and new functions." *Curr. Opin. Cell Biol.* **12**, 174-179 (2000).
- Sonnenburg, W.K. et al. "Identification, quantitation, and cellular localization of PDE1 calmodulin-stimulated cyclic nucleotide phosphodiesterases." *Methods* **14**, 3-19 (1998).
- Teixeira, M.M. et al. "Phosphodiesterase (PDE)4 inhibitors: Anti-inflammatory drugs of the future?" *Trends Pharmacol. Sci.* **18**, 164-170 (1997).
- Zhao, A.Z. et al. "Recent advances in the study of Ca²⁺/CaM activated phosphodiesterases: Expression and physiological functions." *Adv. Second Messenger Phosphoprotein Res.* **31**, 237-251 (1997).
- Zhao, A.Z. et al. "Leptin inhibits insulin secretion by activation of phosphodiesterase 3B." *J. Clin. Invest.* **102**, 869-873 (1998).
- Zhao, A.Z. et al. "Attenuation of insulin secretion by insulin-like growth factor 1 is mediated through activation of phosphodiesterase 3B." *Proc. Natl. Acad. Sci. USA* **94**, 3223-3228 (1997).

Overview

Cyclic nucleotide phosphodiesterases (PDEs) catalyze the hydrolysis of cAMP and/or cGMP. They function in conjunction with adenylyl and guanylyl cyclases to regulate the amplitude and duration of cell signaling mechanisms mediated via cAMP and cGMP. They therefore serve to regulate a range of biological responses to first messengers such as light, hormones, neurotransmitters and odorants. Two classes of functional PDEs (which do not share any sequence homology) are recognized: Class II PDEs have to date only been found in lower eukaryotes and are not as well characterized as Class I PDEs. Class I PDEs are found in all eukaryotic cells, either in the cytoplasm or bound to intracellular organelles or membranes. They all contain an approximately 250 amino acid catalytic domain near the C-terminus that is conserved across families within this class. This overview focuses on the Class I PDEs identified in mammalian cells.

Sequence analyses suggest that there are at least 11 different families of mammalian PDEs, most of which contain more than one gene product. Furthermore, many of these genes can be alternately spliced in a tissue specific manner to give several different mRNAs/proteins with altered regulatory properties or subcellular localization. PDEs are named to precisely identify the isozyme being referenced. For example, MMPDE4A1 refers to the *Mus musculus* PDE4 family, gene A, splice variant 1.

Each PDE family, and even PDEs within a family, can display different substrate specificities, kinetics, allosteric regulation and subcellular localization. Therefore, the expression profile of PDEs within a given

cell will determine which PDEs regulate cyclic nucleotide levels in that cell or subcellular region. The distinct cellular localization and biophysical characteristics of the various PDEs suggest that individual PDEs are individually regulated and play distinct roles in specific physiological processes. For example, the three gene products of the PDE1 family are activated by calcium/calmodulin and are probably inactivated by phosphorylation by protein kinase A and/or calmodulin (CaM) kinase II. They are thought to participate in the feed-forward amplification of neuronal signals. Similarly, PDE2A has been shown to play a role in regulating aldosterone production in adrenal glomerulosa cells through integration of cAMP and cGMP signals. PDE3s, the cGMP-inhibited PDEs, allow cGMP to potentiate a cAMP signal in cells where they are expressed. PDE3A is involved in regulation of platelet aggregation by cGMP, while PDE3B mediates insulin regulation of lipolysis in adipocytes and IGF-1 or leptin inhibition of insulin secretion in pancreatic beta cells. PDE4s (4A, 4B, 4C and 4D) are widely expressed and are likely responsible for modulating a variety of functions, including emesis, lymphocyte-mediated inflammation and follicle stimulating hormone responsiveness in Sertoli cells. PDE5A plays a role in regulating smooth muscle tension in humans, and sildenafil, a selective PDE5A inhibitor, is used as a therapeutic agent to treat erectile dysfunction in man. PDE6A and 6B play a central role in visual phototransduction through rapid modulation of cGMP hydrolysis. PDE7A is induced upon T-cell activation and thought to play a role in modulation of T-cell responsiveness.

The remaining PDEs have only recently been described and specific cellular functions for each isozyme have not been elucidated. Early data suggest that PDE7B may participate in signal transduction in the liver and pancreas. PDE8A is highly expressed in pre-meiotic spermatids, while PDE8B is found almost exclusively in the thyroid. PDE9A is found primarily in the kidney, whereas PDE10A is abundant in the testis and brain. PDE11A is found in skeletal muscle, as well as in the prostate. It is likely that these PDE isozymes play important roles in these tissues. For more information on the individual PDE family members, readers are directed to a regularly updated database on the world wide web (<http://depts.washington.edu/~pde/>).

Cyclic Nucleotide 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 PDEs	cGMP-stimulated PDEs	cGMP-inhibited PDEs	cAMP-specific PDEs	cGMP-binding PDEs	Photoreceptor PDEs
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 (G 6129)	cGMP (G 6129) Insulin (I 5500 (b) , I 0259 (h)) Leptin (L 4146 (h) , L 3772 (m) , L 5037 (r))	PKA (P 5511)	PKG	Light
SUBSTRATE SPECIFICITY	cAMP (A 6885) or cGMP (G 6129)	cAMP (A 6885) or cGMP (G 6129)	cAMP (A 6885) or cGMP (G 6129)	cAMP (A 6885)	cGMP (G 6129)	cGMP (G 6129)
SELECTIVE INHIBITORS ^c	Vinpocetine (V 6383) ^d KS-505a ^{d,e} SCH-51866 ^d	EHNA (E-114)	Milrinone (M 4659) Enoximone (E 1279) Imazodan (I 0782) Trequinsin (T 2057)	Rolipram (R 6520) Ro 20-1724 (B 8279) Etazolate (E 1896) RP 73401 SB-207499	Sildenafil Zaprinast (Z 0878) ^d Dipyridamole (D 9766) ^d T-1032 (T 7692)	Zaprinast (Z 0878) ^d Dipyridamole (D 9766) ^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

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-Hehahydro-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 www.depts.washington.edu/~pde/ for a more complete listing and nomenclature.

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

c Several compounds act as non-selective inhibitors of most cyclic nucleotide phosphodiesterases including 3-isobutyl-1-methylxanthine (IBMX [I 5879](#)), theophylline ([T 1633](#)), papaverine ([P 3510](#)), pentoxifylline ([P 1784](#)) and 1,3-dipropyl-7-methylxanthine ([D-108](#)).

d Note: Truly selective compounds 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.

e For chemical structure of KS-505a, see Ichimura, A. et al. *Biochem. J.* **316**, 311-316 (1996).

Cyclic Nucleotide Phosphodiesterases

FAMILY NAME	PDE7	PDE8	PDE9	PDE10	PDE11
KNOWN GENES ^a	7A, 7B	8A, 8B	9A	10A	11A
DESCRIPTIVE NAME	High affinity cAMP-specific PDEs	cAMP-specific PDEs	High affinity cGMP-specific PDEs	Dual specificity PDEs	Dual specificity PDEs
STRUCTURAL INFORMATION ^b	482 aa (human) HSPDE7A1	713 aa (human) HSPDE8A1	593 aa (human) HSPDE9A1	779 aa (human) HSDPE10A1	490 aa (human) HSPDE11A1
REGULATORS	Unknown	Unknown	Unknown	Unknown	Unknown
SUBSTRATE SPECIFICITY	cAMP (A 6885)	cAMP (A 6885)	cGMP (G 6129)	cAMP (A 6885) or cGMP (G 6129)	cAMP (A 6885) or cGMP (G 6129)
SELECTIVE INHIBITORS ^c	None	Dipyridamole (D 9766) ^d	SCH-51866 ^d	Sildenafil Zaprinast (Z 0878) ^d Dipyridamole (D 9766) ^d SCH-51866 ^d	Zaprinast (Z 0878) ^d Dipyridamole (D 9766) ^d
MAJOR TISSUE EXPRESSION	Skeletal muscle, T-cells	Testis, liver, thyroid	Kidney	Testis, brain	Skeletal muscle, prostate

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