Phosphodiesterases, 3′,5′-cyclic nucleotide (E.C.3.1.4.17)

Overview: 3′,5′-Cyclic nucleotide phosphodiesterases (PDEs, 3′,5′-cyclic-nucleotide 5′-nucleotidohydrolase) catalyse the hydrolysis of a 3′,5′-cyclic nucleotide (usually cyclic AMP or cyclic GMP). IBMX is a nonselective inhibitor with an IC_{50} value in the millimolar range for all isoforms except PDE 8A, 8B and 9A. A 2′,3′-cyclic nucleotide 3′-phosphodiesterase (E.C. 3.1.4.37 CNPase) activity is associated with myelin formation in the development of the CNS.

Nomenclature	PDE1A	PDE1B	PDE1C	PDE2A
Other names	PDE I	PDE I	PDE I	PDE II, cGMP-stimulated cAMP-PDE, CGS-PDE
Ensembl ID	ENSG00000115252	ENSG00000123360	ENSG00000154678	SwissProt O00408
Rank order of affinity	cGMP > cAMP	cGMP > cAMP	cGMP = cAMP	cAMP >> cGMP
Activators	Ca^{2+}/CaM	Ca^{2+}/CaM	Ca^{2+}/CaM	cGMP
Selective inhibitors	SCH51866 (7.2, Vemulapalli *et al.*, 1996), vinpocetine (5.1, Loughney *et al.*, 1996)	SCH51866 (7.2, Vemulapalli *et al.*, 1996)	SCH51866 (7.2, Vemulapalli *et al.*, 1996), vinpocetine (4.3, Loughney *et al.*, 1996)	BAY607550 (8.3–8.8, Boess *et al.*, 2004), EHNA (5.3, Michie *et al.*, 1996)

PDE1A, 1B and 1C appear to act as soluble homodimers, while PDE2A is a membrane-bound homodimer. EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4).

Nomenclature	PDE3A	PDE3B
Other names	PDE III, cGMP-inhibited cAMP-PDE, CGI-PDE A	PDE III, cGMP-inhibited cAMP-PDE, CGI-PDE B
Ensembl ID	ENSG00000172572	ENSG00000152270
Selective inhibitors	Cilostamide (7.5, Sudo *et al.*, 2000), milrinone (6.3, Sudo *et al.*, 2000), cGMP	Cilostamide (7.3, Sudo *et al.*, 2000), milrinone (6.0, Sudo *et al.*, 2000), cGMP

PDE3A and PDE3B are membrane-bound.

Nomenclature	PDE4A	PDE4B	PDE4C	PDE4D
Other names	PDE IV	PDE IV	PDE IV	PDE IV
Ensembl ID	ENSG00000065989	ENSG00000184588	ENSG00000105650	ENSG00000113448
Rank order of affinity	cAMP >> cGMP	cAMP >> cGMP	cAMP >> cGMP	cAMP >> cGMP
Activators	–	–	–	PKA-mediated phosphorylation (Houslay and Adams, 2003)
Selective inhibitors	Rolipram (9.0, Wang *et al.*, 1997), YM976 (8.3, Aoki *et al.*, 2000), Ro201724 (6.5, Wang *et al.*, 1997)	Rolipram (9.0, Wang *et al.*, 1997), Ro201724 (6.4, Wang *et al.*, 1997)	Rolipram (6.5, Wang *et al.*, 1997), Ro201724 (5.4, Wang *et al.*, 1997)	Rolipram (7.2, Wang *et al.*, 1997), Ro201724 (6.2, Wang *et al.*, 1997)

PDE4 isoforms are essentially cAMP specific. The potency of YM976 at other members of the PDE4 family has not been reported. PDE4B–D long forms are inhibited by extracellular signal-regulated kinase (ERK)-mediated phosphorylation (Hoffmann *et al.*, 1998; Hoffmann *et al.*, 1999). PDE4A–D splice variants can be membrane-bound or cytosolic (Houslay and Adams, 2003). PDE4 isoforms may be labelled with [^{3}H]-rolipram.

Nomenclature	PDE5A	PDE7A	PDE7B	PDE8A	PDE8B
Other names	PDE V, cGMP-specific PDE	HCP1	–	High-affinity cAMP-specific and IBMX-insensitive PDE	–
Ensembl ID	ENSG00000138735	ENSG00000104732	ENSG00000171408	ENSG00000073417	ENSG00000113231
Rank order of affinity	cGMP > cAMP	cAMP >> cGMP (Michaeli *et al.*, 1993)	cAMP >> cGMP (Gardner *et al.*, 2000)	cAMP >> cGMP (Fisher *et al.*, 1998a)	cAMP >> cGMP (Hayashi *et al.*, 1998)
Activators	PKA (Corbin *et al.*, 2000), PKG (Corbin *et al.*, 2000)	–	–	–	–
Selective inhibitors	T0156 (9.5, Mochida *et al.*, 2002), sildenafil (9.0, Turko *et al.*, 1999), SCH51866 (7.2, Vemulapalli *et al.*, 1996), zaprinast (6.8, Turko *et al.*, 1999)	BRL50481 (6.7, Smith *et al.*, 2004)	Dipyridamole (5.7–6.0, Gardner *et al.*, 2000); Sasaki *et al.*, 2000), SCH51866 (5.8, Sasaki *et al.*, 2000)	Dipyridamole (5.1, Fisher *et al.*, 1998a)	Dipyridamole (4.3, Hayashi *et al.*, 1998)

PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively. BRL50481 appears not to have been examined as an inhibitor of PDE7B.

Nomenclature	PDE9A	PDE10A	PDE11A
Ensembl ID	ENSG00000160191	ENSG00000112541	ENSG00000128655
Substrate specificity	cGMP >> cAMP (Fisher *et al.*, 1998b)	cAMP, cGMP (Fujishige *et al.*, 1999)	cAMP, cGMP (Fawcett *et al.*, 2000)
Selective inhibitors	BAY736691 (7.3, Wunder *et al.*, 2005)	Papaverine (7.4, Siuciak *et al.*, 2006)	–

Nomenclature	PDE6A	PDE6B	PDE6C	PDE6D	PDE6G	PDE6H
Other names	cGMP-PDE α, PDE V-b1	cGMP-PDE β	cGMP-PDE α, PDEA2	cGMP-PDE δ	cGMP-PDE γ	cGMP-PDE γ
Ensembl ID	ENSG00000132915	ENSG00000133256	ENSG00000095464	ENSG00000156973	ENSG00000185527	ENSG00000139053

PDE6 is a membrane-bound tetramer composed of two catalytic chains (PDE6A or PDE6C and PDE6B), an inhibitory chain (PDE6G or PDE6H) and the PDE6D chain. The enzyme is essentially cGMP specific and is activated by the α-subunit of transducin (G_t) and inhibited by sildenafil, zaprinast and dipyridamole with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.

Abbreviations: **BAY607550**, 2-(3,4-dimethoxybenzyl)-7-{(1R)-1-[(1R)-1-hydroxyethyl]-4-phenylbutyl}-5-methylimidazo[5,1-f][1,2,4]triazin-4(3*H*)-one; 1-**BAY736691**, (2-chlorophenyl)-6-[(2R)-3,3,3-trifluoro-2-methylpropyl]-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidine-4-one; **BRL50481**, 5-nitro-2,*N*,*N*-trimethylbenzenesulfonamide; **EHNA**, *erythro*-9-(2-hydroxy-3-nonyl)adenine; **PKA**, cyclic AMP-dependent protein kinase; **PKG**, cyclic GMP-dependent protein kinase; **Ro201724**, 4-(3-butoxy-4-methoxyphenyl)methyl-2-imidazolidone; **YM976**, (4-[3-chlorophenyl]-1,7-diethylpyrido[2,3-d]pyrimidin-2(1*H*)-one); **SCH51866**, *cis*-5,6*a*,7,8,9,9*a*-hexahydro-2-(4-[trifluoromethyl]phenylmethyl)-5-methyl-cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one

Further Reading

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