SECOND MESSENGER METABOLISING ENZYMES

Cyclooxygenase

Overview: Prostaglandin G/H synthase is most commonly referred to as cyclooxygenase (COX, EC 1.14.99.1, (5*Z*,8*Z*,11*Z*,14*Z*)-icosa-5,8,11,14-tetraenoate,hydrogen-donor:oxygen oxidoreductase) activity, which catalyses the formation of prostaglandin (PG) G_2 from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH_2 from PGG_2. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indomethacin and paracetamol (acetaminophen).

Nomenclature	**COX-1**	**COX-2**
Other names	Prostaglandin G2/H2 synthase-1	Prostaglandin G2/H2 synthase-2
Ensembl ID	ENSG00000095303	ENSG00000073756
Substrates	Arachidonic acid	Arachidonic acid, docosahexaenoic acid
Selective inhibitors	FR122047 (7.5, Ochi *et al*., 2000)	Diclofenac (6.7), celecoxib (5.1), rofecoxib (4.3), valdecoxib, parecoxib, etoricoxib, lumiracoxib

Abbreviation: **FR122047**, 1-([4,5-bis{4-methoxyphenyl}-2-thiazoyl]carbonyl)-4-methylpiperazine hydrochloride

Further Reading:

BAKHLE, Y.S. (2001). COX-2 and cancer: a new approach to an old problem. *Br. J. Pharmacol.,* **134**, 1137–1150.

CATELLA-LAWSON, F., REILLY, M.P., KAPOOR, S.C., CUCCHIARA, A.J., DEMARCO, S., TOURNIER, B., VYAS, S.N. & FITZGERALD, G.A. (2001). Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N. Engl. J. Med.,* **345**, 1809–1817.

DE GAETANO, G., DONATI, M.B. & CERLETTI, C. (2003). Prevention of thrombosis and vascular inflammation: benefits and limitations of selective or combined COX-1, COX-2 and 5-LOX inhibitors. *Trends Pharmacol. Sci.,* **24**, 245–252.

FIORUCCI, S., MELI, R., BUCCI, M. & CIRINO, G. (2001). Dual inhibitors of cyclooxygenase and 5-lipoxygenase. A new avenue in anti-inflammatory therapy? *Biochem. Pharmacol.,* **62**, 1433–1438.

FITZGERALD, G.A. (2003). COX-2 and beyond; approaches to prostaglandin inhibition in human disease. *Nat. Rev. Drug Disc.,* **2**, 879–890.

FITZGERALD, G.A. & PATRONO, C. (2001). The coxibs, selective inhibitors of cyclooxygenase-2. *N. Engl. J. Med.,* **345**, 433–442.

GARG, R., KURUP, A., MEKAPATI, S.B. & HANSCH, C. (2003). Cyclooxygenase (COX) inhibitors: a comparative QSAR study. *Chem. Rev.,* **103**, 703–732.

GUPTA, R.A. & DUBOIS, R.N. (2001). Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. *Nat. Rev. Cancer,* **1**, 11–21.

HAWKEY, C.J. & LANGMAN, M.J. (2003). Non-steroidal anti-inflammatory drugs: overall risks and management. Complementary roles for COX-2 inhibitors and proton pump inhibitors. *Gut,* **52**, 600–608.

HINZ, B. & BRUNE, K. (2002). Cyclooxygenase – 2–10 years later. *J. Pharmacol. Exp. Ther.,* **300**, 367–375.

HWANG, D. (2001). Modulation of the expression of cyclooxygenase-2 by fatty acids mediated through toll-like receptor 4-derived signaling pathways. *FASEB. J.,* **15**, 2556–2564.

MARCUS, A.J., BROEKMAN, M.J. & PINSKY, D.J. (2002). COX inhibitors and thromboregulation. *N. Engl. J. Med.,* **347**, 1025–1026.

MARNETT, L.J. & DUBOIS, R.N. (2002). COX-2: a target for colon cancer prevention. *Annu. Rev. Pharmacol. Toxicol.,* **42**, 55–80.

MORITA, I. (2002). Distinct functions of COX-1 and COX-2. *Prostagland. Other Lipid Mediat.,* **68–69**, 165–175.

PATRONO, C., PATRIGNANI, P. & GARCIA RODRIGUEZ, L.A. (2001). Cyclooxygenase-selective inhibition of prostanoid formation: transducing biochemical selectivity into clinical read-outs. *J. Clin. Invest.,* **108**, 7–13.

SERHAN, C.N. & OLIW, E. (2001). Unorthodox routes to prostanoid formation: new twists in cyclooxygenase-initiated pathways. *J. Clin. Invest.,* **107**, 1481–1489.

SMITH, W.L. & LANGENBACH, R. (2001). Why there are two cyclooxygenase isozymes. *J. Clin. Invest.,* **107**, 1491–1495.

SUBBARAMAIAH, K. & DANNENBERG, A.J. (2003). Cyclooxygenase 2: a molecular target for cancer prevention and treatment. *Trends Pharmacol. Sci.,* **24**, 96–102.

SVENSSON, C.I. & YAKSH, T.L. (2002). The spinal phospholipase-cyclooxygenase-prostanoid cascade in nociceptive processing. *Annu. Rev. Pharmacol. Toxicol.,* **42**, 553–583.

TANABE, T. & TOHNAI, N. (2002). Cyclooxygenase isozymes and their gene structures and expression. *Prostagland. Other Lipid Mediat.,* **68–69**, 95–114.

TEGEDER, I., PFEILSCHIFTER, J. & GEISSLINGER, G. (2001). Cyclooxygenase-independent actions of cyclooxygenase inhibitors. *FASEB J.,* **15**, 2057–2072.

TURINI, M.E. & DUBOIS, R.N. (2002). Cyclooxygenase-2: a therapeutic target. *Annu. Rev. Med.,* **53**, 35–57.

WARNER, T.D. & MITCHELL, J.A. (2002). Cyclooxygenase-3 (COX-3): filling in the gaps toward a COX continuum? *Proc. Natl. Acad. Sci. U.S.A.,* **99**, 13371–13373.

Reference:

OCHI, T. *et al*. (2000). *Eur. J. Pharmacol.,* **391**, 49–54.

Inositol monophosphatase

Overview: Inositol monophosphatase (IMPase, EC 3.1.3.25, *myo*-inositol-1(or 4)-phosphate phosphohydrolase) is a magnesium-dependent homodimer which hydrolyses *myo*-inositol monophosphate to generate *myo*-inositol and phosphate, and is thought to be the molecular target of lithium action in the treatment of bipolar disorder. Glycerol may be a physiological phosphate acceptor. Lithium is a nonselective uncompetitive inhibitor of IMPase (pK_i *ca.* 3.5, McAllister *et al*., 1992). IMPase activity may be inhibited competitively by L690330 (pK_i 5.5, McAllister *et al*., 1992), although the enzyme selectivity is not yet established.

Nomenclature	**IMPase 1**	**IMPase 2**
Other names	IMPA1	IMPA2
Ensembl ID	ENSG00000133731	ENSG00000141401
Rank order of affinity	Inositol 4-phosphate > inositol 3-phosphate > inositol 1-phosphate (McAllister *et al*., 1992)	—

Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder (Sjoholt *et al*., 1997; 2000; Yoshikawa *et al*., 1997).

Abbreviation: L690330, 1-(4-hydroxyphenoxy)ethane-1,1-bisphosphonate

Further Reading:

ATACK, J.R. (1996). Inositol monophosphatase, the putative therapeutic target for lithium. *Brain Res. Rev.,* **22**, 183–190.

ATACK, J.R. (1997). Inositol monophosphatase inhibitors – lithium mimetics? *Med. Res. Rev.,* **17**, 215–224.

ATACK, J.R., BROUGHTON, H.B. & POLLACK, S.J. (1995a). Inositol monophosphatase – a putative target for Li^+ in the treatment of bipolar disorder. *Trends Neurosci.,* **18**, 343–349.

ATACK, J.R., BROUGHTON, H.B. & POLLACK, S.J. (1995b). Structure and mechanism of inositol monophosphatase. *FEBS Lett.,* **361**, 1–7.

IKEDA, A. & KATO, T. (2003). Biological predictors of lithium response in bipolar disorder. *Psychiatry Clin. Neurosci.,* **57**, 243–250.

LENOX, R.H. & WANG, L. (2003). Molecular basis of lithium action: integration of lithium-responsive signaling and gene expression networks. *Mol. Psychiatry,* **8**, 135–144.

PHIEL, C.J. & KLEIN, P.S. (2001). Molecular targets of lithium action. *Annu. Rev. Pharmacol. Toxicol.,* **41**, 789–813.

References:

MCALLISTER, G. *et al*. (1992). *Biochem. J.,* **284**, 749–754.

SJOHOLT, G. *et al*. (1997). *Genomics,* **45**, 113–122.

SJOHOLT, G. *et al*. (2000). *Mol. Psychiatry,* **5**, 172–180.

YOSHIKAWA, T. *et al*. (1997). *Mol. Psychiatry,* **2**, 393–397.

Lipoxygenase

Overview: The lipoxygenases (LOXs) are a structurally related family of nonheme iron dioxygenases that function in the production of fatty acid hydroperoxides. In humans, the 5S- (EC 1.13.11.34, arachidonate:oxygen 5-oxidoreductase), 12S- (EC 1.13.11.31, arachidonate:oxygen 12-oxidoreductase), and 15S- (EC 1.13.11.33, arachidonate:oxygen 15-oxidoreductase) LOXs oxygenate arachidonic acid in different positions along the carbon chain and form the corresponding 5S-, 12S-, or 15S-hydroperoxides, respectively. Some general LOX inhibitors are nordihydroguaiaretic acid (NDGA) and esculetin (6,7-dihydroxycoumarin).

Nomenclature	**5-LOX**	**E-LOX**
Other names	ALOX5	Epidermis type LOX 3
Ensembl ID	ENSG00000012779	ENSG00000179148
Substrates	Arachidonic acid	12R-HPETE
Activators	5-Lipoxygenase-activating protein (FLAP, MK-886-binding protein, ENSG00000132965)	—
Selective inhibitors	Zileuton	—

Nomenclature	**12S-LOX**	**12R-LOX**	**15-LOX**	**15-LOX-2**
Other names	ALOX12, platelet-type 12-lipoxygenase	ALOX12B	ALOX15, arachidonate ω-6 lipoxygenase	ALOX15B
Ensembl ID	ENSG00000108839	ENSG00000179477	ENSG00000161905	ENSG00000179593
Substrates	Arachidonic acid	Methyl arachidonate	Linoleic acid, arachidonic acid	Arachidonic acid

An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 (Furstenberger *et al*., 2002). Caffeic acid is used as a 5-LOX inhibitor, while 5,6,7-trihydroxyflavone (baicalein) and cinnamyl-3,4-dihydroxy-α-cyanocinnamate (CDC) are 12-LOX inhibitors. The specificity of these inhibitors has not been rigorously assessed with all LOX forms.

Abbreviation: **12R-HPETE**, 12R-hydroperoxyeicosatetraenoic acid

Further Reading:

BIGBY, T.D. (2002). The yin and the yang of 5-lipoxygenase pathway activation. *Mol. Pharmacol.,* **62**, 200–202.

BRASH, A.R. (1999). Lipoxygenases: occurrence, functions, catalysis, and acquisition of substrate. *J. Biol. Chem.,* **274**, 23679–23682.

DE GAETANO, G., DONATI, M.B. & CERLETTI, C. (2003). Prevention of thrombosis and vascular inflammation: benefits and limitations of selective or combined COX-1, COX-2 and 5-LOX inhibitors. *Trends Pharmacol. Sci.,* **24**, 245–252.

FEINMARK, S.J. & CORNICELLI, J.A. (1997). Is there a role for 15-lipoxygenase in atherogenesis? *Biochem. Pharmacol.,* **54**, 953–959.

FIORUCCI, S., MELI, R., BUCCI, M. & CIRINO, G. (2001). Dual inhibitors of cyclooxygenase and 5-lipoxygenase. A new avenue in anti-inflammatory therapy? *Biochem. Pharmacol.,* **62**, 1433–1438.

FUNK, C.D. & CHEN, X.S. (2000). 5-Lipoxygenase and leukotrienes. Transgenic mouse and nuclear targeting studies. *Am. J. Respir. Crit. Care Med.,* **161**, S120–S124.

FUNK, C.D., CHEN, X.S., JOHNSON, E.N. & ZHAO, L. (2002). Lipoxygenase genes and their targeted disruption. *Prostagland. Other Lipid Mediat.,* **68–69**, 303–312.

FUNK, C.D. & CYRUS, T. (2001). 12/15-lipoxygenase, oxidative modification of LDL and atherogenesis. *Trends Cardiovasc. Med.,* **11**, 116–124.

FURSTENBERGER, G., MARKS, F. & KRIEG, P. (2002). Arachidonate 8(S)-lipoxygenase. *Prostagland. Other Lipid Mediat.,* **68–69**, 235–243.

GAFFNEY, B.J., BOYINGTON, J.C., AMZEL, L.M., DOCTOR, K.S., PRIGGE, S.T. & YUAN, S.M. (1995). Lipoxygenase structure and mechanism. *Adv. Prostagland. Thromboxane Leukotr. Res.,* **23**, 11–16.

KITA, T. (1999). LOX-1, a possible clue to the missing link between hypertension and atherogenesis. *Circ. Res.,* **84**, 1113–1115.

KUHN, H. & THIELE, B.J. (1999). The diversity of the lipoxygenase family. Many sequence data but little information on biological significance. *FEBS Lett.,* **449**, 7–11.

MANEV, H., UZ, T., SUGAYA, K. & QU, T. (2000). Putative role of neuronal 5-lipoxygenase in an aging brain. *FASEB J.,* **14**, 1464–1469.

NASSER, S.M. & LEE, T.H. (2002). Products of 15-lipoxygenase: are they important in asthma? *Clin. Exp. Allergy,* **32**, 1540–1542.

NIE, D. & HONN, K.V. (2002). Cyclooxygenase, lipoxygenase and tumor angiogenesis. *Cell Mol. Life Sci.,* **59**, 799–807.

RADMARK, O. (2002). Arachidonate 5-lipoxygenase. *Prostagland. Other Lipid Mediat.,* **68-69**, 211–234.

RADMARK, O.P. (2000). The molecular biology and regulation of 5-lipoxygenase. *Am. J. Respir. Crit. Care Med.,* **161**, S11–S15.

WEN, Y., GU, J., PENG, X., ZHANG, G. & NADLER, J. (2003). Overexpression of 12-lipoxygenase and cardiac fibroblast hypertrophy. *Trends Cardiovasc. Med.,* **13**, 129–136.

Reference:

FURSTENBERGER, G. *et al*. (2002). *Prostagland. Other Lipid Mediat.,* **68–69**, 235–243.

Nitric oxide synthase

Overview: The nomenclature suggested by IUPHAR of NOS I, II and III (see Moncada *et al*., 1997) has not gained wide acceptance. Nitric oxide synthases (NOS, EC 1.14.13.39, L-arginine, $NADPH_2$:oxygen oxidoreductase (nitric-oxide-forming)) utilise L-arginine (not D-arginine) and molecular oxygen to generate nitric oxide and L-citrulline. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for Ca^{2+}/calmodulin and thus appears to be constitutively active. All the three isoforms are homodimers and require tetrahydrobiopterin, flavin adenine dinucleotide, flavin mononucleotide and NADPH for catalytic activity. L-NAME is an inhibitor of all the three isoforms, with an IC_{50} value in the micromolar range.

Nomenclature	**Endothelial NOS**	**Inducible NOS**	**Neuronal NOS**
Preferred abbreviation	eNOS	iNOS	nNOS
Other names	NOS III, NOS-3, ecNOS	NOS II, NOS-2	NOS I, NOS-1, brain NOS
Ensembl ID	ENSG00000164867	ENSG00000007171	ENSG00000089250
Selective inhibitors	—	1400W (8.2, Garvey *et al*., 1997), 2-amino-4-methylpyridine (7.4, Faraci *et al*., 1996), PIBTU (7.3, Garvey *et al*., 1994), NIL (5.5, Moore *et al*., 1994), aminoguanidine (Corbett & McDaniel, 1992)	3-bromo-7NI (6.1-6.5, Bland-Ward & Moore, 1995), 7NI (5.3, Babbedge *et al*., 1993)

The reductase domain of NOS catalyses the reduction of cytochrome *c* and other redox-active dyes (Mayer and Hemmens, 1997). NADPH:O_2 oxidoreductase catalyses the formation of superoxide anion/H_2O_2 in the absence of arginine and tetrahydrobiopterin.

Abbreviations: **NADPH**, reduced nicotinamide adenosine dinucleotide phosphate; **7NI**, 7-nitroindazole; **NIL**, L-N^6-(1-iminoethyl)lysine; **PIBTU**, 13-phenylen-bis(1,2ethanediyl)bis-thiourea; **1400W**, *N*-(3-[aminomethyl]benzyl)acetamidine

Further Reading:

ALDERTON, W.K., COOPER, C.E. & KNOWLES, R.G. (2001). Nitric oxide synthases: structure, function and inhibition. *Biochem. J.,* **357**, 593–615.

ANDREW, P.J. & MAYER, B. (1999). Enzymatic function of nitric oxide synthases. *Cardiovasc. Res.,* **43**, 521–531.

CHRISTOPOULOS, A. & EL-FAKAHANY, E.E. (1998). The generation of nitric oxide by G protein-coupled receptors. *Life Sci.,* **64**, 1–15.

HOBBS, A.J., HIGGS, A. & MONCADA, S. (1999). Inhibition of nitric oxide synthase as a potential therapeutic target. *Annu. Rev. Pharmacol. Toxicol.,* **39**, 191–220.

MAYER, B. & HEMMENS, B. (1997). Biosynthesis and action of nitric oxide in mammalian cells. *Trends Biochem. Sci.,* **22**, 477–481.

MONCADA, S. (1999). Nitric oxide: discovery and impact on clinical medicine. *J. R. Soc. Med.,* **92**, 164–169.

MOORE, P.K. & HANDY, R.L.C. (1997). Selective inhibitors of neuronal nitric oxide synthase – is no NOS really good NOS for the nervous system? *Trends Pharmacol. Sci.,* **18**, 204–211.

MUSCARA, M.N. & WALLACE, J.L. (1999). Nitric oxide V. Therapeutic potential of nitric oxide donors and inhibitors. *Am. J. Physiol. Gastrointest. Liver Physiol.,* **276**, G1313–G1316.

SHAUL, P.W. (2002). Regulation of endothelial nitric oxide synthase: location, location, location. *Annu. Rev. Physiol.,* **64**, 749–774.

References:

BABBEDGE, R.C. *et al*. (1993). *Br. J. Pharmacol.,* **110**, 225–228.

BLAND-WARD, P.A. & MOORE, P.K. (1995). *Life Sci.,* **57**, PL131–PL135.

CORBETT, J.A. & MCDANIEL, M.L. (1992). *Diabetes,* **41**, 897–903.

FARACI, W.S. *et al*. (1996). *Br. J. Pharmacol.,* **119**, 1101–1108.

GARVEY, E.P. *et al*. (1994). *J. Biol. Chem.,* **269**, 26669–26676.

GARVEY, E.P. *et al*. (1997). *J. Biol. Chem.,* **272**, 4959–4963.

MAYER, B. & HEMMENS, B. (1997). *Trends Biochem. Sci.,* **22**, 477–481.

MOORE, W.M. *et al*. (1994). *J. Med. Chem.,* **37**, 3886–3888.

3′,5′-Cyclic nucleotide phosphodiesterase

Overview: 3′,5′-Cyclic nucleotide phosphodiesterases (PDEs, EC 3.1.4.17, 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′-PDE (EC 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)	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 (EC 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 & Adams, 2003)
Selective inhibitors	Rolipram (9.0, Wang *et al*., 1997), 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. PDE4B–D long forms are inhibited by extracellular signal-regulated kinase (ERK)-mediated phosphorylation (Hoffmann *et al*., 1998; 1999). PDE4A–D splice variants can be membrane-bound or cytosolic (Houslay & Adams, 2003).

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	Sildenafil (9.0, Turko *et al*., 1999), SCH51866 (7.2, Vemulapalli *et al*., 1996), zaprinast (6.8, Turko *et al*., 1999)	—	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.

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.

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	SCH51866 (5.8, Fisher *et al*., 1998b), zaprinast (4.5, Fisher *et al*., 1998b)	—	—

Abbreviations: **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; **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:

BURNOUF, C. & PRUNIAUX, M.P. (2002). Recent advances in PDE4 inhibitors as immunoregulators and anti-inflammatory drugs. *Curr. Pharm. Des.,* **8**, 1255–1296.

CONTI, M., RICHTER, W., MEHATS, C., LIVERA, G., PARK, J.Y. & JIN, C. (2003). Cyclic AMP-specific PDE4 phosphodiesterases as critical components of cyclic AMP signaling. *J. Biol. Chem.,* **278**, 5493–5496.

CONTI, S.L.C. & JIN, M. (1999) The molecular biology of cyclic nucleotide phosphodiesterases. *Prog. Nucleic Acid Res. Mol. Biol.,* **63**, 1–38.

FELDMAN, A.M. & MCNAMARA, D.M. (2002). Reevaluating the role of phosphodiesterase inhibitors in the treatment of cardiovascular disease. *Clin. Cardiol.,* **25**, 256–262.

GROOTENDORST, D.C. & RABE, K.F. (2002). Selective phosphodiesterase inhibitors for the treatment of asthma and chronic obstructive pulmonary disease. *Curr. Opin. Allergy Clin. Immunol.,* **2**, 61–67.

HANING, H., NIEWOHNER, U. & BISCHOFF, E. (2003). Phosphodiesterase type 5 (PDE5) inhibitors. *Prog. Med. Chem.,* **41**, 249–306.

HOUSLAY, M.D. & ADAMS, D.R. (2003). PDE4 cAMP phosphodiesterases: modular enzymes that orchestrate signalling cross-talk, desensitization and compartmentalization. *Biochem. J.,* **370**, 1–18.

KUTHE, A., MONTORSI, F., ANDERSSON, K.E. & STIEF, C.G. (2002). Phosphodiesterase inhibitors for the treatment of erectile dysfunction. *Curr. Opin. Investig. Drugs,* **3**, 1489–1495.

MANGANIELLO, V. (2003). Cyclic nucleotide phosphodiesterase 5 and sildenafil: promises realized. *Mol. Pharmacol.,* **63**, 1209–1211.

MAURICE, D.H., PALMER, D., TILLEY, D.G., DUNKERLEY, H.A., NETHERTON, S.J., RAYMOND, D.R., ELBATARNY, H.S. & JIMMO, S.L. (2003). Cyclic nucleotide phosphodiesterase activity, expression, and targeting in cells of the cardiovascular system. *Mol. Pharmacol.,* **64**, 533–546.

REFFELMANN, T. & KLONER, R.A. (2003). Therapeutic potential of phosphodiesterase 5 inhibition for cardiovascular disease. *Circulation,* **108**, 239–244.

ROTELLA, D.P. (2002). Phosphodiesterase 5 inhibitors: current status and potential applications. *Nat. Rev. Drug Discov.,* **1**, 674–682.

SCHULTZ, A., STUCK, B.A., FEURING, M., HORMANN, K. & WEHLING, M. (2003). Novel approaches in the treatment of allergic rhinitis. *Curr. Opin. Allergy Clin. Immunol.,* **3**, 21–27.

SHAKUR, Y., HOLST, L.S., LANDSTROM, T.R., MOVSESIAN, M., DEGERMAN, E. & MANGANIELLO, V. (2001). Regulation and function of the cyclic nucleotide phosphodiesterase (PDE3) gene family. *Prog. Nucleic Acid Res. Mol. Biol.,* **66**, 241–277.

SODERLING, S.H. & BEAVO, J.A. (2000) Regulation of cAMP and cGMP signaling: new phosphodiesterases and new functions. *Curr. Opin. Cell Biol.,* **12**, 174–179.

SPINA, D. (2003). Theophylline and PDE4 inhibitors in asthma. *Curr. Opin. Pulmon. Med.,* **9**, 57–64.

References:

CORBIN, J.D. *et al*. (2000). *Eur. J. Biochem.,* **267**, 2760–2767.

FAWCETT, L. *et al*. (2000). *Proc. Natl. Acad. Sci. U.S.A.,* **97**, 3702–3707.

FISHER, D.A. *et al*. (1998a). *Biochem. Biophys. Res. Commun.,* **246**, 570–577.

FISHER, D.A. *et al*. (1998b). *J. Biol. Chem.,* **273**, 15559–15564.

FUJISHIGE, K. *et al*. (1999). *J. Biol. Chem.,* **274**, 18438–18445.

GARDNER, C. *et al*. (2000). *Biochem. Biophys. Res. Commun.,* **272**, 186–192.

HAYASHI, M. *et al*. (1998). *Biochem. Biophys. Res. Commun.,* **250**, 751–756.

HOFFMANN, R. *et al*. (1998). *Biochem. J.,* **333**, 139–149.

HOFFMANN, R. *et al*. (1999). *EMBO J.,* **18**, 893–903.

HOUSLAY, M.D. & ADAMS, D.R. (2003). *Biochem. J.,* **370**, 1–18.

LOUGHNEY, K. *et al*. (1996). *J. Biol. Chem.,* **271**, 796–806.

MICHAELI, T. *et al*. (1993). *J. Biol. Chem.,* **268**, 12925–12932.

MICHIE, A.M. *et al*. (1996). *Cell. Signal,* **8**, 97–110.

SASAKI, T. *et al*. (2000). *Biochem. Biophys. Res. Commun.,* **271**, 575–583.

SUDO, T. *et al*. (2000). *Biochem. Pharmacol.,* **59**, 347–356.

TURKO, I.V. *et al*. (1999). *Mol. Pharmacol.,* **56**, 124–130.

VEMULAPALLI, S. *et al*. (1996). *J. Cardiovasc. Pharmacol.,* **28**, 862–869.

WANG, P. *et al*. (1997). *Biochem. Biophys. Res. Commun.,* **234**, 320–324.

Soluble guanylyl cyclase

Overview: Soluble guanylyl cyclase (sGC, EC 4.6.1.2, GTP diphosphate-lyase (cyclizing)) is a heterodimer comprising α and β chains, both of which have two subtypes in man (predominantly $\alpha1\beta1$, see Zabel *et al*., 1998). A haem group is associated with the α chain and is the target for the endogenous ligand nitric oxide ($NO^{\bullet}$), and, potentially, carbon monoxide (Friebe *et al*., 1996).

Nomenclature	**Soluble guanylyl cyclase**
Ensembl ID	$\alpha1$ ENSG00000164116; $\alpha2$ ENSG00000152402; $\beta1$ ENSG00000061918; $\beta2$ ENSG00000123201
Selective stimuli	$NO^{\bullet}$, YC-1 (Friebe *et al*., 1996)
Selective inhibitors	ODQ (7.5, Garthwaite *et al*., 1995)

ODQ also shows activity at other haem-containing proteins (Feelisch *et al*., 1999).

Abbreviations: **ODQ**, 1*H*-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one; **YC-1**, 3-(5′-hydroxymethyl-2′-furyl)-1-benzylindazole

Further Reading:

DAVIS, K.L., MARTIN, E., TURKO, I.V. & MURAD, F. (2001). Novel effects of nitric oxide. *Annu. Rev. Pharmacol. Toxicol.,* **41**, 203–236.

DENNINGER, J.W. & MARLETTA, M.A. (1999). Guanylate cyclase and the NO/cGMP signaling pathway. *Biochim. Biophys. Acta Bioenerget.,* **1411**, 334–350.

FRIEBE, A. & KOESLING, D. (2003). Regulation of nitric oxide-sensitive guanylyl cyclase. *Circ. Res.,* **93**, 96–105.

HOBBS, A.J. (1997). Soluble guanylate cyclase: the forgotten sibling. *Trends Pharmacol. Sci.,* **18**, 484–491.

KOESLING, D. & FRIEBE, A. (1999). Soluble guanylyl cyclase: structure and regulation. *Rev. Physiol. Biochem. Pharmacol.,* **135**, 41–65.

LUCAS, K.A., PITARI, G.M., KAZEROUNIAN, S., RUIZ-STEWART, I., PARK, J., SCHULZ, S., CHEPENIK, K.P. & WALDMAN, S.A. (2000). Guanylyl cyclases and signaling by cyclic GMP. *Pharmacol. Rev.,* **52**, 375–414.

SITARAMAYYA, A. (2002). Soluble guanylate cyclases in the retina. *Mol. Cell. Biochem.,* **230**, 177–186.

ZABEL, U., WEEGER, M., LA, M. & SCHMIDT, H.H.H.W. (1998). Human soluble guanylate cyclase: functional expression and revised isoenzyme family. *Biochem. J.,* **335**, 51–57.

References:

FEELISCH, M. *et al*. (1999). *Mol. Pharmacol.,* **56**, 243–253.

FRIEBE, A. *et al*. (1996). *EMBO J.,* **15**, 6863–6868.

GARTHWAITE, J. *et al*. (1995). *Mol. Pharmacol.,* **48**, 184–188.