

SECOND MESSENGER METABOLISING ENZYMES

Cyclooxygenase

Overview: Prostaglandin G/H synthase, most commonly referred to as cyclooxygenase (COX, E.C. 1.14.99.1, (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate,hydrogen-donor:oxygen oxidoreductase) activity, catalyses the formation of prostaglandin (PG) G₂ from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH₂ from PGG₂. COX-1 and -2 can be non-selectively inhibited by ibuprofen, ketoprofen, naproxen, indometacin and paracetamol (acetaminophen).

Nomenclature	COX-1	COX-2
Other names	Prostaglandin G ₂ /H ₂ synthase-1	Prostaglandin G ₂ /H ₂ synthase-2
Ensembl ID	ENSG00000095303	ENSG00000073756
Substrates	Arachidonic acid	Arachidonic acid, docosahexaenoic acid
Selective inhibitors	SC560 (8.1, Smith <i>et al.</i> , 1998), FR122047 (7.5, Ochi <i>et al.</i> , 2000)	Diclofenac (6.7), celecoxib (5.1), rofecoxib (4.3), valdecoxib, parecoxib, etoricoxib, lumiracoxib

Abbreviations: **FR122047**, 1-([4,5-bis(methoxyphenyl)-2-thazolyl]carbonyl)-4-methylpiperazine hydrochloride; **SC560**, 5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-trifluoromethylpyrazole

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Inositol monophosphatase

Overview: Inositol monophosphatase (IMPase, E.C. 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. Glycerol may be a physiological phosphate acceptor. Lithium is a non-selective 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 <i>et al.</i> , 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).

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

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Lipoxygenase

Overview: The lipoxygenases (LOXs) are a structurally related family of non-heme iron dioxygenases that function in the production, and in some cases metabolism, of fatty acid hydroperoxides. In humans, the 5S- (E.C. 1.13.11.34, arachidonate:oxygen 5-oxidoreductase), 12S- (E.C. 1.13.11.31, arachidonate:oxygen 12-oxidoreductase), 12R- (E.C. 1.13.11.-, arachidonate 12-lipoxygenase, 12R-type), and 15S- (E.C. 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-, 12R-, or 15S-hydroperoxides, respectively. The epidermal lipoxygenase 3 (E-LOX) metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxyalcohol compound (Yu *et al.*, 2004). 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, CJ13610 (Fischer <i>et al.</i> , 2004)	—

Nomenclature	12S-LOX	12R-LOX	15-LOX-1	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 baicalein (5,6,7-trihydroxyflavone) and CDC (cinnamyl-3,4-dihydroxy- α -cyanocinnamate) are 12-LOX inhibitors. The specificity of these inhibitors has not been rigorously assessed with all LOX forms: baicalein, along with other flavonoids, such as fisetin and luteolin, also inhibits 15-LOX-1 (Sadik *et al.*, 2003).

Abbreviations: **CJ13610**, 1-carboxamido-1-(3-*S*-[4-{2-methylimidazole}-thiophenyl])-4-cyclopentylether; **12R-HPETE**, 12R-hydroperoxyeicosatetraenoic acid

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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, E.C. 1.14.13.39, L-arginine:NADPH₂: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 Ca²⁺/calmodulin and thus appears to be constitutively active. All three isoforms are homodimers and require tetrahydrobiopterin, flavin adenine dinucleotide, flavin mononucleotide and NADPH for catalytic activity. L-NAME is an inhibitor of all three isoforms with an IC₅₀ 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 <i>et al.</i> , 1997), 2-amino-4-methylpyridine (7.4, Faraci <i>et al.</i> , 1996), PIBTU (7.3, Garvey <i>et al.</i> , 1994), NIL (5.5, Moore <i>et al.</i> , 1994), aminoguanidine (Corbett & McDaniel, 1992)	3-bromo-7NI (6.1–6.5, Bland-Ward & Moore, 1995), 7NI (5.3, Babbedge <i>et al.</i> , 1993), GW273629, GW274150 (Young <i>et al.</i> , 2000), VNIO (Babu <i>et al.</i> , 1998)

The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes (Mayer & Hemmens, 1997). NADPH:O₂ oxidoreductase catalyses the formation of superoxide anion/H₂O₂ in the absence of arginine and tetrahydrobiopterin.

Abbreviations: **1400W**, *N*-(3-(aminomethyl) benzyl) acetamide; **7NI**, 7-nitroindazole; **GW273629**, 3-([2-(ethanimidoylamino)ethyl]sulphonyl)-L-alanine; **GW274150**, (S)-2-amino-(1-iminoethylamino)-5-thiopentanoic acid; **NADPH**, reduced nicotinamide adenine dinucleotide phosphate; **NIL**, L-N⁶-(1-iminoethyl)lysine; **PIBTU**, 13-phenyl-bis(1,2-ethanediy)bis-thiourea; **VNIO**, N⁵-(1-imino-3-butenyl)-L-ornithine

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Phosphodiesterase, 3',5'-cyclic nucleotide

Overview: 3',5'-Cyclic nucleotide phosphodiesterases (PDEs, E.C. 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 IC₅₀ 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 <i>et al.</i> , 1996), vinpocetine (5.1, Loughney <i>et al.</i> , 1996)	SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996)	SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996), vinpocetine (4.3, Loughney <i>et al.</i> , 1996)	EHNA (5.3, Michie <i>et al.</i> , 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 <i>et al.</i> , 2000), milrinone (6.3, Sudo <i>et al.</i> , 2000), cGMP	Cilostamide (7.3, Sudo <i>et al.</i> , 2000), milrinone (6.0, Sudo <i>et al.</i> , 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 <i>et al.</i> , 1997), Ro201724 (6.5, Wang <i>et al.</i> , 1997)	Rolipram (9.0, Wang <i>et al.</i> , 1997), Ro201724 (6.4, Wang <i>et al.</i> , 1997)	Rolipram (6.5, Wang <i>et al.</i> , 1997), Ro201724 (5.4, Wang <i>et al.</i> , 1997)	Rolipram (7.2, Wang <i>et al.</i> , 1997), Ro201724 (6.2, Wang <i>et al.</i> , 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; Hoffmann *et al.*, 1999). PDE4A–D splice variants can be membrane-bound or cytosolic (Houslay and 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 <i>et al.</i> , 1993)	cAMP >> cGMP (Gardner <i>et al.</i> , 2000)	cAMP >> cGMP (Fisher <i>et al.</i> , 1998a)	cAMP >> cGMP (Hayashi <i>et al.</i> , 1998)
Activators	PKA (Corbin <i>et al.</i> , 2000), PKG (Corbin <i>et al.</i> , 2000)	—	—	—	—
Selective inhibitors	Sildenafil (9.0, Turko <i>et al.</i> , 1999), SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996), zaprinast (6.8, Turko <i>et al.</i> , 1999)	—	Dipyridamole (5.7–6.0, Gardner <i>et al.</i> , 2000; Sasaki <i>et al.</i> , 2000), SCH51866 (5.8, Sasaki <i>et al.</i> , 2000)	Dipyridamole (5.1, Fisher <i>et al.</i> , 1998a)	Dipyridamole (4.3, Hayashi <i>et al.</i> , 1998)

PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively.

Nomenclature	PDE9A	PDE10A	PDE11A
Ensembl ID	ENSG00000160191	ENSG00000112541	ENSG00000128655
Substrate specificity	cGMP $\gg$ cAMP (Fisher <i>et al.</i> , 1998b)	cAMP, cGMP (Fujishige <i>et al.</i> , 1999)	cAMP, cGMP (Fawcett <i>et al.</i> , 2000)
Selective inhibitors	SCH51866 (5.8, Fisher <i>et al.</i> , 1998b), zaprinast (4.5, Fisher <i>et al.</i> , 1998b)	—	—

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_i) and inhibited by sildenafil, zaprinast and dipyrindamole with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.

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*-5,6a,7,8,9,9a-hexahydro-2-(4-[trifluoromethyl]phenylmethyl)-5-methyl-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one

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Soluble guanylyl cyclase

Overview: Soluble guanylyl cyclase (sGC, E.C. 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 $\alpha 1\beta 1$, see Zabel *et al.*, 1998). A haem group is associated with the α chain and is the target for the endogenous ligand nitric oxide ($\text{NO}^\bullet$), and, potentially, carbon monoxide (Friebe *et al.*, 1996).

Nomenclature	Soluble guanylyl cyclase
Ensembl ID	$\alpha 1$ ENSG00000164116; $\alpha 2$ ENSG00000152402; $\beta 1$ ENSG00000061918; $\beta 2$ ENSG00000123201
Selective stimuli	$\text{NO}^\bullet$, YC-1 (Friebe <i>et al.</i> , 1996)
Selective inhibitors	ODQ (7.5, Garthwaite <i>et al.</i> , 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

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