Adenosine metabolising enzymes

Overview: Adenosine is a multifunctional, ubiquitous molecule that acts at cell-surface 7TM receptors, as well as numerous enzymes, including protein kinases and adenylyl cyclase. Extracellular adenosine accumulates either by export or metabolism, predominantly through ecto-5′-nucleotidase activity (also producing inorganic phosphate). It is inactivated either by extracellular metabolism *via* adenosine deaminase (producing ammonia as a second product) or, following uptake by nucleoside transporters, *via* adenosine deaminase or adenosine kinase (requiring ATP as co-substrate). Intracellular metabolism may be enacted by cytosolic 5′-nucleotidases or through *S*-adenosylhomocysteine hydrolase (producing homocysteine as a second product).

Nomenclature	Adenosine deaminase	Adenosine kinase	Ecto-5′-Nucleotidase	S-Adenosylhomocysteine hydrolase
E.C.	3.5.4.4	2.7.1.20	3.1.3.5	3.3.1.1
Preferred abbreviation	ADA	ADK	NT5E	SAHH
Other names	Adenosine aminohydrolase	—	CD73, 5′-NT	Adenosylhomocysteinase
Ensembl ID	ENSG00000196839	ENSG00000156110	ENSG00000135318	ENSG00000101444
Rank order of affinity	2′-Deoxyadenosine > adenosine	Adenosine	5′-AMP, 5′-GMP, 5′-IMP, 5′-UMP > 5′-dAMP, 5′-dGMP	*S*-Adenosylhomocysteine
Products	2′-Deoxyinosine, inosine	5′-AMP	Adenosine, guanine, inosine, uridine	Adenosine
Selective inhibitors	EHNA, 2′-deoxycoformycin	A134974 (pIC_{50} 10.2, McGaraughty *et al*., 2001), ABT702 (pIC_{50} 8.8, Jarvis *et al*., 2000)	αβ-methyleneADP	—

Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: ADAT1 (ENSG00000065457) deaminates transfer RNA; ADAR (ENSG00000160710, EC 3.5.4.—, also known as 136 kDa double-stranded RNA-binding protein, P136, K88DSRBP, interferon-inducible protein 4); ADARB1 (ENSG00000197381, EC 3.5.-.-, also known as dsRNA adenosine deaminase) and ADARB2 (ENSG00000185736, EC 3.5.-.-, also known as dsRNA adenosine deaminase B2, RNA-dependent adenosine deaminase 3) act on double-stranded RNA. Particular polymorphisms of the ADA gene result in loss-of-function and severe combined immunodeficiency syndrome. Adenosine deaminase is able to complex with dipeptidyl peptidase IV (EC 3.4.14.5, also known as T-cell activation antigen CD26, TP103, adenosine deaminase complexing protein 2, ENSG00000197635) to form a cell-surface activity (Kameoka *et al*., 1993).
Cytosolic 5′-nucleotidase may be divided into IA (ENSG00000116981, NT5C1A), IB (ENSG00000185013, NT5C1B), II (ENSG00000076685, NT5C2), III (ENSG00000122643, NT5C3) and 5′(3′)-nucleotidases (ENSG00000125458, NT5C), together with a mitochondrial isoform (ENSG00000205309, NT5 M).

Abbreviations: 5′-AMP, adenosine 5′-monophosphate; **5′NT**, 5′-nucleotidase; **A134974**, N^7-[(1′R,2′S,3′R,4′S)-2′,3′-dihydroxy-4′-aminocyclopentyl]-4-amino-5-iodopyrrolopyrimidine; **ABT702**, 4-amino-5-(3-bromophenyl)-7-(6-morpholinopyridin-3-yl)pyrido[2,3-d]pyrimidine; **ADA**, adenosine deaminase; **ADK**, adenosine kinase; **EHNA**, *erythro*-9-(2-hydroxy-3-nonyl)adenine hydrochloride

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Adenylyl cyclases (E.C. 4.6.1.1)

Overview: Adenylyl cyclase (ENSF00000000188) converts 5′-ATP to 3′,5′-adenosine monophosphate and pyrophosphate. Mammalian membrane-bound adenylyl cyclases are typically made up of two clusters of six transmembrane domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators forskolin, NKH477 (except AC9, Premont *et al.*, 1996) and Gαs (the stimulatory G protein α subunit). Adenosine and its derivatives (e.g. 2′,5′-dideoxyadenosine), acting through the P-site, appears to be a physiological inhibitor of adenylyl cyclase activity (Tesmer *et al.*, 2000). Three families of adenylyl cyclase are distinguishable: Ca^{2+}/CaM-stimulated (AC1, AC3 and AC8), Ca^{2+}-inhibitable (AC5 and AC6) and Ca^{2+}-insensitive (AC2, AC4 and AC7) forms.

Nomenclature	AC1	AC2	AC3	AC4	AC5
Other names	AC I	AC II, HBCA2	AC III, olfactory type	AC IV	AC V
Ensembl ID	ENSG00000164742	ENSG00000078295	ENSG00000138031	ENSG00000129467	ENSG00000173175
Endogenous activators	Ca^{2+}/CaM (Tang *et al.*, 1991), PKC-evoked phosphorylation (Jacobowitz *et al.*, 1993)	Gβγ (Taussig *et al.*, 1993), PKC-evoked phosphorylation (Chen and Iyengar, 1993; Lustig *et al.*, 1993)	Ca^{2+}/CaM (Choi *et al.*, 1992), PKC-evoked phosphorylation (Jacobowitz *et al.*, 1993)	Gβγ (Gao and Gilman, 1991)	PKC-evoked phosphorylation (Kawabe *et al.*, 1994)
Endogenous inhibitors	Gαi (Taussig *et al.*, 1994), Gαo (Taussig *et al.*, 1994), Gβγ (Taussig *et al.*, 1993)	—	Gαi (Taussig *et al.*, 1994), RGS2 (Sinnarajah *et al.*, 2001), CaM kinase II-evoked phosphorylation (Wayman *et al.*, 1995)	PKC-evoked phosphorylation (Zimmermann and Taussig, 1996)	Gαi (Taussig *et al.*, 1994), Ca^{2+} (Ishikawa *et al.*, 1992), PKA-evoked phosphorylation (Iwami *et al.*, 1995)
Selective inhibitors	—	—	—	—	NKY80 (Onda *et al.*, 2001)

Nomenclature	AC6	AC7	AC8	AC9
Other names	AC VI, Ca^{2+}-inhibitable cyclase	AC VII	AC VIII	AC IX
Ensembl ID	ENSG00000174233	ENSG00000121281	ENSG00000155897	ENSG00000162104
Endogenous activators	—	PKC-evoked phosphorylation (Watson *et al.*, 1994)	Ca^{2+} (Cali *et al.*, 1994)	—
Endogenous inhibitors	Gαi (Taussig *et al.*, 1994), Ca^{2+} (Yoshimura and Cooper, 1992), PKA-evoked phosphorylation (Chen *et al.*, 1997), PKC-evoked phosphorylation (Lai *et al.*, 1999)	—	—	Ca^{2+}/calcineurin (Paterson *et al.*, 2000)

Nitric oxide has been proposed to inhibit AC5 and AC6 selectively (Hill *et al.*, 2000), although it is unclear whether this phenomenon is of physiological significance. A soluble adenylyl cyclase has been described (ENSG00000143199, Buck *et al.*, 1999), unaffected by either Gα or Gβγ subunits, which has been suggested to be a cytoplasmic bicarbonate (pH-insensitive) sensor (Chen *et al.*, 2000).

Abbreviations: CaM, calmodulin; **NKH477**, 6-(3-dimethylaminopropionyl) forskolin hydrochloride; **NKY80**, 2-amino-7-(2-furanyl)-7,8-dihydro-5(6*H*)-quinazolinone; **PKA**, protein kinase A or cyclic AMP-dependent protein kinase; **PKC**, protein kinase C; **RGS2**, Regulator of G-protein signalling 2 (ENSG00000116741)

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Amino acid hydroxylases (E.C.1.14.16.-)

Overview: The amino acid hydroxylases (monooxygenases) are iron-containing enzymes which utilise molecular oxygen and tetrahydrobiopterin as co-substrate and co-factor, respectively.

Nomenclature	L-Phenylalanine hydroxylase	L-Tryptophan hydroxylase	L-Tyrosine hydroxylase
E.C.	1.14.16.1	1.14.16.4	1.14.16.2
Preferred abbreviation	PH	TPH	TH
Other names	Phenylalanine 4-monooxygenase	Tryptophan 5-monooxygenase	Tyrosine 3-monooxygenase
Ensembl ID	ENSG00000171759	TPH1 ENSG00000129167; TPH2 ENSG00000139287	ENSG00000180176
Product	Tyrosine	5-Hydroxytryptophan	DOPA
Selective inhibitors	α-Methylphenylalanine (Greengard *et al*., 1976), PCPA	Fenfluramine, PCPA, α-propyldopacetamide, 6-fluorotryptophan (Nicholson and Wright, 1981)	3-Chlorotyrosine, 3-iodotyrosine, α-methyltyrosine, α-propyldopacetamide

Abbreviations: **DOPA**, 3, 4-dihydroxyphenylalanine; **PCPA**, 4-chlorophenylalanine

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Cyclooxygenase (E.C. 1.14.99.1)

Overview: Prostaglandin (PG) G/H synthase, most commonly referred to as cyclooxygenase (COX, (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate,hydrogen-donor:oxygen oxidoreductase) activity, catalyses the formation of PGG_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, 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	FR122047 (7.5, Ochi *et al*., 2000), valeroylsalicylate (Bhattacharyya *et al*., 1995)	Diclofenac (6.7), celecoxib (5.1), rofecoxib (4.3), valdecoxib, parecoxib, etoricoxib, lumiracoxib

Abbreviations: FR122047, 1-([4,5-bis{methoxyphenyl}-2-thazoyl]carbonyl)-4-methyl)piperazine hydrochloride

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Decarboxylases (E.C. 4.1.1.-)

Overview: The decarboxylases generate CO_2 and the indicated products from acidic substrates, requiring pyridoxal phosphate (ADC, AADC, GAD, HDC, ODC and PSDC or pyruvate (SAMDC and PSDC) as a co-factor. The activity of ODC is regulated by the presence of an antizyme (ENSF00000002504) and an ODC antizyme inhibitor (ENSF00000002504).

Nomenclature	S-Adenosylmethionine decarboxylase	L-Arginine decarboxylase	L-Aromatic amino-acid decarboxylase	Glutamic acid decarboxylase
E.C.	4.1.1.50	4.1.1.19	4.1.1.28	4.1.1.15
Preferred abbreviation	SAMDC	ADC	AADC	GAD
Other names	—	Ornithine decarboxylase- like protein (Zhu *et al.*, 2004)	DOPA decarboxylase (DDC), 5-hydroxytryptophan decarboxylase	GAD1 (GAD65), GAD2 (GAD67)
Ensembl ID	ENSG00000123505	ENSG00000142920	ENSG00000132437	ENSG00000128683, ENSG00000136750
Substrate(s)	S-Adenosylmethionine	L-Arginine	DOPA, L-tryptophan, 5-hydroxy-L-tryptophan	L-Glutamate, L-aspartate
Product(s)	5′-Deoxyadenosyl- (3-aminopropyl) methylsulfonium	Agmatine	5-Hydroxytryptamine, dopamine	GABA
Selective inhibitors	SAM486A (8.0; Stanek *et al.*, 1993), AMA	—	Benserazide, carbidopa, 3-hydroxybenzylhydrazine, L-α-methyldopa	S-Allylglycine

The presence of a functional ADC activity in human tissues has been questioned (Coleman *et al.*, 2004). *s*-Allylglycine is also an inhibitor of SAMDC (Pajunen *et al.*, 1979).

Nomenclature	Histidine decarboxylase	Ornithine decarboxylase	Phosphatidylserine decarboxylase
E.C.	4.1.1.22	4.1.1.17	4.1.1.65
Preferred abbreviation	HDC	ODC	PSDC
Ensembl ID	ENSG00000140287	ENSG00000115758	ENSG00000100141
Substrate(s)	L-Histidine	L-Ornithine	Phosphatidylserine
Product	Histamine	Putrescine	Phosphatidylethanolamine
Selective inhibitors	FMH (Garbarg *et al.*, 1980)	DFMO, APA	—

Abbreviations: AMA, S-(5′-deoxy-5′-adenosyl)-methylthioethyl-hydroxylamine; **APA**, 1-aminooxy-3-aminopropane; **DFMO**, α-difluoromethyl-**L**-ornithine, also known as eflornithine; **FMH**, α-fluoromethylhistidine; **SAM**, S-adenosylmethionine; **SAM486A**, 1-guanidinoimino-2,3-dihydroindene-4-carboximidamide also known as CGP48664

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Endocannabinoid metabolising enzymes

Overview: the principal endocannabinoids are 2-arachidonoylglycerol (2AG) and anandamide (*N*-arachidonoylethanolamine, AEA), thought to be generated primarily by diacylglycerol lipase (DAGL) and *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD). Aside from oxidative metabolism by cyclooxygenase and lipoxygenase enzymes, inactivation of these endocannabinoids appears to occur predominantly through monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH), respectively.

Nomenclature	Diacylglycerol lipase α	Diacylglycerol lipase β	*N*-Acylphosphatidylethanolamine-phospholipase D
Preferred abbreviation	DAGLα	DAGLβ	NAPE-PLD
E.C.	3.1.1._	3.1.1._	—
Other names	Neural stem cell-derived dendrite regulator	KCCR13L	—
Ensembl ID	ENSG00000134780	ENSG00000164535	ENSG00000161048
Selective inhibitors (pIC_{50})	Tetrahydrolipstatin (7.2, Bisogno *et al*., 2003), RHC80267	Tetrahydrolipstatin (7.0, Bisogno *et al*., 2003), RHC80267	—

NAPE-PLD activity appears to be enhanced by polyamines in the physiological range (Liu *et al*., 2002), but fails to transphosphatidylate with alcohols (Petersen and Hansen, 1999) unlike phosphatidylcholine-specific phospholipase D.

Nomenclature	Monoacylglycerol lipase	Fatty acid amide hydrolase-1	Fatty acid amide hydrolase-2	*N*-Acylethanolamine acid amidase
Preferred abbreviation	MAGL	FAAH1	FAAH2	NAAA
E.C.	3.1.1.23	3.1._._	3.1._._	3.5.1._
Other names	HU-K5, lysophospholipase homolog	Oleamide hydrolase, anandamide hydrolase	—	Acid ceramidase-like protein, *N*-acylsphingosine amidohydrolase-like, N-palmitoylethanolamine acid amidase
Ensembl ID	ENSG00000074416	ENSG00000117480	ENSG00000165591	ENSG00000138744
Potency order	2OG = 2AG > AEA (Ghafouri *et al*., 2004)	AEA > ODA > OEA > PEA > NOT (Wei *et al*., 2006)	ODA > OEA > AEA > PEA (Wei *et al*., 2006)	PEA > MEA > SEA > OEA > AEA (Ueda *et al*., 2001)
Selective inhibitors (pIC_{50})	—	URB597 (6.3-7.0, Wei *et al*., 2006), OL135 (7.4, Wei *et al*., 2006)	URB597 (7.5-8.3, Wei *et al*., 2006), OL135 (7.9, Wei *et al*., 2006)	CCP (5.3, Tsuboi *et al*., 2004)

A pharmacologically-distinct MAGL has recently been described in microglial cells (Muccioli *et al*., 2007). URB602 was initially described as a selective MAGL inhibitor (Hohmann *et al*., 2005), although a subsequent study suggested it possessed significant inhibitory potency at FAAH1 (Vandevoorde *et al*., 2007). URB754 also showed initial promise as a selective MAGL inhibitor (Makara *et al*., 2005), although a corrigendum ascribed MAGL inhibition to a contaminant (Makara *et al*., 2007).

Abbreviations: **2AG**, 2-arachidonoylglycerol; **2OG**, 2-oleoylglycerol; **AEA**, anandamide; **CCP**, *N*-cyclohexylcarbonylpentadecylamine; **DAGL**, diacylglycerol lipase; **FAAH**, fatty acid amide hydrolase; **MAGL**, monoacylglycerol lipase; **MEA**, *N*-myristoylethanolamine; **NAAA**, *N*-acylethanolamine acid amidase; **NAPE-PLD**, *N*-acylphosphatidylethanolamine-phospholipase D; **NOT**, *N*-oleoyltaurine; **ODA**, octadec(9,10*z*) enamide; **OEA**, *N*-oleoylethanolamine; **OL135**, 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-phenylheptane; **PEA**, *N*-palmitoylethanolamine; **RHC80267**, 1,6-bis(cyclohexyloximinocarbonylamino)hexane; **SEA**, *N*-stearoylethanolamine; **URB597**, cyclohexyl carbamic acid 3′-carbamoyl-biphenyl-3-yl ester; **URB602**, [1,1′-biphenyl]-3-yl-carbamic acid, cyclohexyl ester; **URB754**, 6-methyl-2-*p*-tolylaminobenzo[*d*]oxazin-4-one

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Inositol monophosphatase (E.C. 3.1.3.25)

Overview: Inositol monophosphatase (IMPase, *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 nonselective un-competitive 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; Yoshikawa *et al.*, 1997; Sjoholt *et al.*, 2000).

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

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Lipoxygenases (E.C. 1.13.11.-)

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 there are five lipoxygenases, the 5*S*-(arachidonate : oxygen 5-oxidoreductase), 12*R*-(arachidonate 12-lipoxygenase, 12*R*-type), 12*S*-(arachidonate : oxygen 12-oxidoreductase), and two distinct 15*S*-(arachidonate : oxygen 15-oxidoreductase) LOXs that oxygenate arachidonic acid in different positions along the carbon chain and form the corresponding 5*S*-, 12*S*-, 12*R*-, or 15*S*-hydroperoxides, respectively. The sixth lipoxygenase member, epidermal lipoxygenase 3 (E-LOX), metabolises the product from the 12*R*-lipoxygenase (12*R*-HPETE) to a specific epoxyalcohol compound (Yu *et al*., 2003). Some general LOX inhibitors are NDGA and esculetin.

Nomenclature	5-LOX	12R-LOX	12S-LOX
E.C.	1.13.11.34	1.13.11.-	1.13.11.31
Other names	ALOX5	ALOX12B	ALOX12, platelet-type 12-lipoxygenase
Ensembl ID	ENSG00000012779	ENSG00000179477	ENSG00000108839
Substrates	Arachidonic acid	Methyl arachidonate	Arachidonic acid
Activators	FLAP	—	—
Selective inhibitors	Zileuton, CJ13610 (Fischer *et al*., 2004)	—	—

Nomenclature	15-LOX-1	15-LOX-2	E-LOX
E.C.	1.13.11.33	1.13.11.33	1.13.11.-
Other names	ALOX15, arachidonate ω-6 lipoxygenase	ALOX15B	Epidermis type LOX 3
Ensembl ID	ENSG00000161905	ENSG00000179593	ENSG00000179148
Substrates	Linoleic acid, arachidonic acid	Arachidonic acid	12*R*-HPETE

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). Zileuton and caffeic acid are used as 5-lipoxygenase inhibitors, while baicalein and CDC are 12-lipoxygenase 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: CDC, cinnamyl-3,4-dihydroxy-α-cyanocinnamate; **CJ13610**, 1-carboxamido-1-(3-*S*-[4-{2-methylimididazole}-thiophenyl])-4-cyclopentylether; **esculetin**, 6,7-dihydroxycoumarin; **12*R*-HPETE**, 12*R*-hydroperoxyeicosatetraenoic acid; **FLAP**, 5-lipoxygenase-activating protein, also known as MK-886-binding protein (ENSG00000132965); **NDGA**, nordihydroguaiaretic acid

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Nitric oxide synthase (E.C. 1.14.13.39)

Overview: The nomenclature suggested by NC-IUPHAR of NOS I, II and III (see Moncada *et al.*, 1997) has not gained wide acceptance. Nitric oxide synthases (NOS, 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 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 and McDaniel, 1992)	3-Bromo-7NI (6.1-6.5, Bland-Ward and 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: 1400W, *N*-(3-(aminomethyl) benzyl)acetamidine; **NADPH**, reduced nicotinamide adenosine dinucleotide phosphate; **7NI**, 7-nitroindazole; **NIL**, L-N^6-(1-iminoethyl)lysine; **PIBTU**, 13-phenylen-bis(1,2ethanediyl)bis-thiourea

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Phosphatidylcholine-specific phospholipase D (E.C. 3.1.4.4)

Overview: Phosphatidylcholine-specific phospholipase D (PLD, ENSF00000001451) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction (Randall *et al.*, 1990).

Nomenclature	PLD1	PLD2
Other names	Choline phosphatase 1	Choline phosphatase 2
Ensembl ID	ENSG00000075651	ENSG00000129219
Endogenous activators	ARF, PIP_2, RhoA, PKC-evoked phosphorylation (Hammond *et al.*, 1997)	ARF, PIP_2 (Lopez *et al.*, 1998), oleic acid (Sarri *et al.*, 2003)

A lysophospholipase D activity (ENSG00000136960, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), phosphodiesterase I, nucleotide pyrophosphatase 2, autotaxin) has been described, which not only catalyses the production of lysophosphatidic acid from lysophosphatidylcholine, but also cleaves ATP (see Goding *et al.*, 2003). Additionally, an *N*-acylethanolamine-specific phospholipase D (NAPE-PLD, ENSG00000161048) has recently been characterized, which appears to have a role in the generation of endocannabinoids/endovanilloids, including anandamide (Okamoto *et al.*, 2004). This enzyme activity appears to be enhanced by polyamines in the physiological range (Liu *et al.*, 2002) and fails to transphosphatidylate with alcohols (Petersen and Hansen, 1999).

Abbreviations: ARF, ADP-ribosylation factor; **NAPE-PLD**, *N*-acylethanolamine-specific phospholipase D; **PIP_2**, phosphatidylinositol 4,5-bisphosphate

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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	ENSG00000186642
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 & 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	SCH51866 (5.8, Fisher *et al*., 1998b), zaprinast (4.5, Fisher *et al*., 1998b)	—	—

Nomenclature	PDE6A	PDE6B	PDE6C	PDE6D	PDE6G	PDE6 H
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

Abbreviations: BAY607550, 2-(3,4-dimethoxybenzyl)-7-{(1R)-1-[(1R)-1-hydroxyethyl]-4-phenylbutyl}-5-methylimidazo[5,1-f][1,2,4]triazin-4(^3H)-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(1H)-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(3H)-one

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Phospholipase A_2 (E.C. 3.1.1.4)

Overview: Phospholipase A_2 (PLA_2) cleaves the *sn*-2 fatty acid of phospholipids, primarily phosphatidylcholine, to generate lysophosphatidylcholine and arachidonic acid. Most commonly-used inhibitors (e.g. BEL, ATFMK or MAFP) are either non-selective within the family of phospholipase A_2 enzymes or have activity against other eicosanoid-metabolising enzymes.

Secreted or extracellular forms

Nomenclature	GIB	GIIA	GIID	GIIE	GIIF	GIII
Other names	PLA2G1B, pancreatic PLA_2	PLA2G2A, GIIC sPLA2, non-pancreatic secretory phospholipase A_2, NPS-PLA_2, synovial PLA_2	PLA2G2D, GIID $sPLA_2$, secretory-type PLA_2, stroma-associated homolog	PLA2G2E, GIIE $sPLA_2$	PLA2G2F, GIIF $sPLA_2$	GIII $sPLA_2$
Ensembl ID	ENSG00000170890	ENSG00000188257	ENSG00000117215	ENSG00000188784	ENSG00000158786	ENSG00000100078

PLA2G2C may be a pseudogene. A further fragment has been identified with sequence similarities to Group II PLA_2 members (ENSG00000187980).

Cytosolic, calcium-dependent forms

Nomenclature	GIVA	GIVB	GIVC	GIVD	GIVE	GIVF
Other names	PLA2G4A, Calcium-dependent PLA_2, cytosolic phospholipase A_2	PLA2G4B, cytosolic phospholipase A_2 β	PLA2G4C, cytosolic phospholipase A_2 γ	PLA2G4D, cytosolic phospholipase A_2 δ	PLA2G4E, cytosolic phospholipase A_2 ε	PLA2G4F, cytosolic phospholipase A_2 ζ
Ensembl ID	ENSG00000116711	ENSG00000168970	ENSG00000105499	ENSG00000159337	ENSG00000188089	ENSG00000168907

PLA_2-GIVA also expresses lysophospholipase (EC 3.1.1.5) activity (Sharp *et al.*, 1994).

Other forms

Nomenclature	GV	GVI	GVII	GX	GXIIA	GXIIB
Other names	PLA2G5, PLA_2-10	PLA2G6, Ca^{2+}-independent, $iPLA_2$, PNPLA9	PLA2G7, LDL-associated phospholipase A_2	PLA2G10, GX $sPLA_2$	PLA2G12A, GXII $sPLA_2$	PLA2G12B, GXIII $sPLA_2$-like
Ensembl ID	ENSG00000127472	ENSG00000184381	ENSG00000146070	ENSG00000069764	ENSG00000123739	ENSG00000138308

PLA_2-GVII and a close homologue (HSD-PLA_2, also known as serine-dependent phospholipase A_2, PAFAH2, ENSG00000158006) also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47). Otoconin 90 (OC90, ENSG00000132297) shows sequence homology to PLA_2-GX.

Abbreviations: ATFMK, arachidonoyltrifluoromethylketone; **BEL**, bromoenolactone; **MAFP**, methylarachidonoylfluorophosphonate; **PLA_2**, phospholipase A_2

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Phosphoinositide-specific phospholipase C (E.C. 3.1.4.11)

Overview: Phosphoinositide-specific phospholipase C (PLC) catalyses the hydrolysis of phosphatidylinositol 4,5-bisphosphate to inositol 1,4,5-trisphosphate and 1,2-diacylglycerol, each of which have major second messenger functions. Two domains, X and Y, essential for catalytic activity, are conserved in the different forms of PLC. Isoforms of PLC-β (ENSF00000000466) are activated primarily by 7TM receptors through members of the $G_{q/11}$ family of G proteins. The receptor-mediated activation of PLC-γ involves their phosphorylation by tyrosine kinases in response to activation of a variety of growth factor receptors and immune system receptors. PLC-ε1 may represent a point of convergence of signalling via both 7TM and catalytic receptors. Ca^{2+} ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC-δ activity. PLC has been suggested to be activated non-selectively by the small molecule *m*-3M3FBS (Bae *et al*., 2003), although this mechanism of action has been questioned (Krjukova *et al*., 2004). The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC (Smith *et al*., 1990), although its selectivity among the isoforms is untested and it has been reported to occupy the H_1 histamine receptor (Hughes *et al*., 2000).

Nomenclature	β1	β2	β3	β4
Other names	PLC-I, PLC-154, KIAA0581	—	—	—
Ensembl ID	ENSG00000182621	ENSG00000137841	ENSG00000149782	ENSG00000101333
Endogenous activators	Gαq (Smrcka *et al*., 1991; Hepler *et al*., 1993), Gα11 (Hepler *et al*., 1993), Gβγ (Park *et al*., 1993)	Gα16 (Lee *et al*., 1992), Gβγ (Camps *et al*., 1992; Park *et al*., 1993)	Gαq (Lee *et al*., 1992), Gβγ (Carozzi *et al*., 1993; Park *et al*., 1993)	Gαq (Jhon *et al*., 1993)

Nomenclature	γ1	γ2	δ1	δ3	δ4
Other names	PLC-II, PLC-148	PLC-IV	PLC-III	—	—
Ensembl ID	ENSG00000124181	ENSG00000197943	ENSG00000187091	ENSG00000161714	ENSG00000115556
Endogenous activators	PtdIns 3,4,5-P_3 (Bae *et al*., 1998)	PtdIns 3,4,5-P_3 (Bae *et al*., 1998)	Transglutaminase II (Murthy *et al*., 1999), p122-RhoGAP (Homma and Emori, 1995), spermine (Haber *et al*., 1991), Gβγ (Park *et al*., 1993)	—	—
Inhibitors	—	—	Sphingomyelin (Pawelczyk and Lowenstein, 1992)	—	—

PLC-δ2 has been cloned from bovine sources (Meldrum *et al*., 1991).

Nomenclature	ε1	ζ1	η1	η2
Other names	Pancreas-enriched PLC	—	—	—
Ensembl/GenBank ID	ENSG00000138193	ENSG00000139151	AY691170 (Hwang *et al*., 2005)	DQ176850 (Zhou *et al*., 2005)
Endogenous activators	Ras (Song *et al*., 2001), Rho (Wing *et al*., 2003)	—	—	Gβγ (Zhou *et al*., 2005)

A series of PLC-like proteins (PLCL1 ENSG00000115896; PLCL2 ENSG00000154822 and PLCL3 ENSG00000114805) form a family (ENSF00000000386) with PLCδ and PLCζ1 isoforms, but appear to lack catalytic activity.

Abbreviations: m-3M3FBS, 2,4,6-trimethyl-*N*-(*meta*-3-trifluoromethylphenyl)-benzenesulphonamide; **Ptdlns** 3,4,5-P_3, phosphatidylinositol 3,4,5-trisphosphate; **U73122**, 1-(6-[{(17β)-3-methoxyestra-1,3,5[10]-trien-17-yl}amino]hexyl)-1*H*-pyrrole-2,5-dione

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Protein serine/threonine kinases (E.C. 2.7.1.37)

Overview: Protein serine/threonine kinases use the co-substrate ATP to phosphorylate serine and/or threonine residues on target proteins. Most inhibitors of these enzymes have been assessed in cell-free investigations and so may appear to 'lose' potency and selectivity in intact cell assays. In particular, ambient ATP concentrations may be influential in responses to inhibitors, since the majority are directed at the ATP binding site (see Davies *et al.*, 2000; Bain *et al.*, 2007).

It is beyond the scope of the Guide to list all protein kinase activities; this summary focusses on protein kinases involved in signalling from 7-transmembrane receptors.

Nomenclature	Protein kinase A	Protein kinase B	Protein kinase G	Rho kinase
Preferred abbreviation	PKA	PKB	PKG	—
Other names	Cyclic AMP-dependent protein kinase	Akt	Cyclic GMP-dependent protein kinase	P160ROCK, Rho-activated kinase
Ensembl ID	Regulatory subunits: PRKAR1A (ENSG00000108946); PRKAR1B (ENSG00000188191); PRKAR2A (ENSG00000114302); PRKAR2B (ENSG00000005249); Catalytic subunits: PRKACA (ENSG00000072062); PRKACB (ENSG00000142875); PRKACG (ENSG00000165059)	AKT1 (ENSG00000142208); AKT2 (ENSG00000105221); AKT3 (ENSG00000117020)	PRKG1 (ENSG00000185532); PRKG2 (ENSG00000138669)	ROCK1 (ENSG00000067900); ROCK2 (ENSG00000134318)
Endogenous activator	cAMP	PDK1 (Alessi *et al.*, 1997)	cGMP	Rho
Selective activators	N^6-Benzyl-cAMP (Christensen *et al.*, 2003)	—	—	—
Selective inhibitors	Rp-cAMPS	—	Rp-8-CPT-cGMPS (Butt *et al.*, 1994)	Y27632 (Uehata *et al.*, 1997), fasudil (Asano *et al.*, 1989)
Probes	[^{3}H]-cAMP	—	—	—

PKA is a heterotetrameric enzyme composed of two regulatory and two catalytic subunits, which can be distinguished from Epac (exchange protein directly activated by cAMP, de Rooij *et al.*, 1998) by differential activation by N^6-benzyl-cAMP and CPT-2′OMe-cAMP, respectively (Kang *et al.*, 2005). AKT1 and AKT2 can be selectively inhibited by AKT 1/2 inhibitor with pIC_{50} values of 7.3 and 6.8, respectively (Zhao *et al.*, 2005), while deguelin (Chun *et al.*, 2003), API2 (Yang *et al.*, 2004) and Akt inhibitor IV (Kozikowski *et al.*, 2003) can inhibit PKB activity by inhibiting activation by upstream kinases.

Protein kinase C

Protein kinase C is the target for the tumour-promoting phorbol esters, such as tetradecanoyl-β-phorbol acetate (TPA).
Classical protein kinase C isoforms: Members of the classical protein kinase C family are activated by Ca2+ and diacylglycerol, and may be inhibited by GF109203X, calphostin C, Gö6983, chelerythrine and Ro318220.

Nomenclature	PKCα	PKCβ1	PKCβ2	PKCγ
Other names	PRKCA	PRKCB1	PRKCB2	PRKCG
Ensembl ID	ENSG00000154229	ENSG00000166501	ENSG00	ENSG00000126583
Selective inhibitors	—	Ruboxistaurin (8.3, Jirousek *et al.*, 1996), CGP53353 (6.4, Chalfant *et al.*, 1996)	Ruboxistaurin (8.2, Jirousek *et al.*, 1996)	—

Novel protein kinase C isoforms: Members of the classical protein kinase C family are activated by diacylglycerol and may be inhibited by calphostin C, Gö6983 and chelerythrine.

Nomenclature	PKCδ	PKCε	PKCη	PKCθ	PKCμ
Other names	PRKCD	PRKCE	PRKCH	PRKCQ	KPCD1, nPKC-D1, protein kinase D
Ensembl ID	ENSG00000163932	ENSG00000171132	ENSG00000027075	ENSG00000065675	ENSG00000184304

Atypical protein kinase C isoforms

Nomenclature	PKCζ	PKCι	PKN
Other names	PRKCZ	PRKCI (PKCλ in rodents)	PRK, Protein kinase N1, protein kinase C-related kinase 1
Ensembl ID	ENSG00000067606	ENSG00000163558	ENSG00000123143
Endogenous activator	Arachidonic acid	—	Rho, PIP_3

Mitogen-activated protein kinases (MAP kinases)

Nomenclature	ERK1	ERK2	JNK1	JNK2	JNK3
HUGO Nomenclature	MAPK3	MAPK1	MAPK8	MAPK9	MAPK10
Other names	Insulin-stimulated MAP2 kinase, ERT2, p44-MAPK, Microtubule-associated protein-2 kinase	Mitogen-activated protein kinase 2, p42-MAPK, ERT1	SAPK1, c-Jun N-terminal kinase 1, JNK-46	c-Jun N-terminal kinase 2, JNK-55	c-Jun N-terminal kinase 3, MAP kinase p49 3F12
Ensembl ID	ENSG00000102882	ENSG00000100030	ENSG00000107643	ENSG00000050748	ENSG00000109339
Endogenous activator	MAP2K1, MAP2K2	MAP2K1, MAP2K2	MAP2K4, MAP2K7	MAP2K4, MAP2K7	MAP2K4, MAP2K7
Selective inhibitors	—	—	SP600125 (6.7, Bennett *et al*., 2001)	SP600125 (6.7, Bennett *et al*., 2001)	SP600125 (6.7, Bennett *et al*., 2001)

MAP kinases (CMGC kinases, ENSF00000000137) may be divided into three major families: ERK1/2, JNK and p38 MAP kinases.
The inhibitors PD98059 (Alessi *et al*., 1995; Dudley *et al*., 1995) and U0126 (Duncia *et al*., 1998; Favata *et al*., 1998) are used as selective inhibitors of ERK1 and ERK2, but have been shown rather to target the upstream kinase cascade (Davies *et al*., 2000).
MAP2K1 (ENSG00000169032, EC 2.7.12.2) and MAP2K2 (ENSG00000126934, EC 2.7.12.2) are also known as MAP kinase kinase 1 and 2, or MEK1 and MEK2, respectively. MAP2K4 (ENSG00000065559, EC 2.7.12.2) and MAP2K7 (ENSG00000076984, EC 2.7.12.2) are also known as JNK-activating kinase 1 and 2 or JNKK1 and JNKK2, respectively.

Nomenclature	p38α	p38β	p38γ	p38δ
HUGO Nomenclature	MAPK14	MAPK11	MAPK12	MAPK13
Other names	Cytokine suppressive anti-inflammatory drug binding protein, MAX-interacting protein 2	p38-2, SAPK2	ERK-6, ERK5, SAPK3	SAPK4
Ensembl ID	ENSG00000112062	ENSG00000185386	ENSG00000188130	ENSG00000156711
Endogenous activator	MAP2K3, MAP2K6	MAP2K3, MAP2K6	MAP2K3, MAP2K6	MAP2K3, MAP2K6
Selective inhibitors	SB203580 (8.0, Eyers *et al*., 1998)	SB203580 (7.0, Eyers *et al*., 1998)	—	—

MAP2K3 (ENSG00000034152, EC 2.7.12.2) and MAP2K6 (ENSG00000108984, EC 2.7.12.2) are also known as MAP kinase kinase 3 and MAP kinase kinase 6, respectively.

Selected other protein kinase activities

Nomenclature	AMP kinase	Myosin light chain kinase 1	Myosin light chain kinase 2	Calmodulin-dependent kinase II
Preferred abbreviation	AMPK	MLCK1	MLCK2	CaMKII
Other names	—	MYLK, smooth muscle and non-muscle isoform	MYLK, skeletal muscle isoform	—
Ensembl ID	α1 (ENSG00000132356); α2 (ENSG00000162409); β1 (ENSG00000111725); β2 (ENSG00000131791); γ1 (ENSG00000181929), γ2 (ENSG00000106617); γ3 (ENSG00000115592)	ENSG00000065534	ENSG00000101306	α (ENSG00000070808); β (ENSG00000058404); γ (ENSG00000148660); δ (ENSG00000145349)
Endogenous activator	AMP	Ca^{2+}-calmodulin	Ca^{2+}-calmodulin	Ca^{2+}-calmodulin
Selective activators	AICA-riboside Corton *et al*. (1995)	—	—	—

AMP-activated protein kinase is a heterotrimeric protein kinase, made up of α, β and γ subunits. STO609 is an inhibitor of calmodulin kinase kinase (EC 2.7.11.17, Tokumitsu *et al*., 2002), an upstream activator of calmodulin-dependent kinase.

Abbreviations: **AICA-riboside**, 5-aminoimidazole-4-carboxamide-1-β-riboside, also known as acadesine; **AKT1/2**, 1,3-dihydro-1-(1-[{4-(6-phenyl-1H-imidazo[4,5-g]quinoxalin-7-yl)phenyl}methyl]-4-piperidinyl)-2H-benzimidazol-2-one trifluoroacetate salt hydrate; **Akt inhibitor IV**, 5-(2-benzothiazolyl)-3-ethyl-2-(2-[methylphenylamino]ethenyl)-1-phenyl-1H-benzimidazolium iodide; **API2**, 1,5-dihydro-5-methyl-1-β-D-ribofuranosyl-1,4,5,6,8-pentaazaacennaphthylen-3-amine, also known as triciribine; **CGP53353**, 5,6-bis([4-fluorophenyl]amino)-2*H*-isoindole-1,3-dione; **CPT-2′-OMe-cAMP**, 8-(4-chlorophenylthio)-2-O-methyladenosine 3,5-cyclic monophosphate monosodium hydrate; **fasudil**, 1-(5-isoquinolinylsulfonyl)homopiperazine dihydrochloride, also known as HA1077; **PD98059**, 2-(2-amino-3-methoxy-phenyl)chromen-4-one; **PDK1**, 3-phosphoinoisitide-dependent protein kinase 1 (EC 2.7.11.1) ENSG00000140992; **Rp-8-CPT-cGMPS**, Rp-8-[(4-chlorophenyl)thio]-guanosine-cyclic 3,5-hydrogen phosphorothioate; **ruboxistaurin**, (s)-13-[(dimethylamino)methyl]-10,11,14,15-tetrahydro-4,9:16,21-dimetheno-1*H*,13*H*-dibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecene-1,3(2*H*)-dione, also known as LY333531; **SB203580**, 4-(5-[4-fluorophenyl]-2-[4-methylsulfinylphenyl]-3*H*-imidazol-4-yl)pyridine; **SP600125**, anthra[1,9-*cd*]pyrazol-6(2*H*)-one; **STO609**, 7-oxo-7*H*-benzimidazo(2,1a) benz(de)isoquinoline-3-carboxy acid acetate; **Y27632**, (*R*)-(+)-*trans*-4-(1-aminoethyl)-*N*-(4-pyridyl)cyclohexanecarboxamide dihydrochloride monohydrate

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Soluble guanylyl cyclase (E.C. 4.6.1.2)

Overview: Soluble guanylyl cyclase (GTP diphosphate-lyase (cyclising)) 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 β chain and is the target for the endogenous ligand nitric oxide ($NO^{\bullet}$), and, potentially, carbon monoxide (Friebe *et al.*, 1996). The enzyme converts guanosine-5′-triphosphate (GTP) to the intracellular second messenger 3′,5′-guanosine monophosphate (cGMP).

Nomenclature	Soluble guanylyl cyclase
Preferred abbreviation	sGC
Ensembl ID	α1 ENSG00000164116; α2 ENSG00000152402; β1 ENSG00000061918; β2 ENSG00000123201
Selective activators	$NO^{\bullet}$, YC1 (Friebe *et al.*, 1996), BAY412272 (Stasch *et al.*, 2001), BAY582667 (Stasch *et al.*, 2002)
Selective inhibitors	ODQ (7.5; Garthwaite *et al.*, 1995)

ODQ also shows activity at other haem-containing proteins (Feelisch *et al.*, 1999), while YC1 may also inhibit cGMP-hydrolysing phosphodiesterases (Friebe *et al.* 1998; Galle *et al.*, 1999).

Abbreviations: BAY412272, 5-cyclopropyl-2-[1-(2-fluoro-benzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-pyrimidin-4-ylamine); **BAY582667**, 4-([4-carboxybutyl][2-{(4-phenethylbenzyl)oxy}phenethyl]amino)methyl(benzoic)acid; **ODQ**, 1*H*-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one; **YC1**, 3-(5′-hydroxymethyl-2′-furyl)-1-benzylindazole HMR1766

Further Reading

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