THE CONCISE GUIDE TO PHARMACOLOGY 2013/14: ENZYMES

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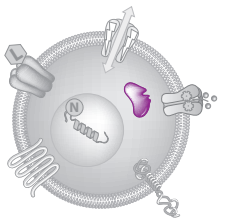

Abstract

The Concise Guide to PHARMACOLOGY 2013/14 provides concise overviews of the key properties of over 2000 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full.

Enzymes are one of the seven major pharmacological targets into which the Guide is divided, with the others being G protein-coupled receptors, ligand-gated ion channels, ion channels, nuclear hormone receptors, catalytic receptors and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. A new landscape format has easy to use tables comparing related targets.

It is a condensed version of material contemporary to late 2013, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in previous Guides to Receptors and Channels. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and the Guide to Receptors and Channels, providing a permanent, citable, point-in-time record that will survive database updates.

An Introduction to Enzymes

Enzymes are protein catalysts facilitating the conversion of substrates into products. The Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB) classifies enzymes into families, using a four number code, on the basis of the reactions they catalyse. There are six main families:

EC 1.-.-.- Oxidoreductases;
EC 2.-.-.- Transferases;
EC 3.-.-.- Hydrolases;
EC 4.-.-.- Lyases;
EC 5.-.-.- Isomerases;
EC 6.-.-.- Ligases.

Although there are many more enzymes than receptors in biology, and many drugs that target prokaryotic enzymes are effective medicines, overall the number of enzyme drug targets is relatively small [1,2], which is not to say that they are of modest importance. In the Concise Guide to PHARMACOLOGY 2013/14, enzymes are presented as a group involved in metabolic pathways (for example, of the neurotransmitters acetylcholine, GABA and dopamine). An alternative grouping for presentation is epitomized by the cytochrome P450 enzymes, which essentially conduct the same enzymatic function, albeit on a very diverse range of substrates.

The majority of drugs which act on enzymes act as inhibitors; one exception is metformin, which appears to stimulate activity of AMP-activated protein kinase, albeit through an imprecisely-defined mechanism. Kinetic assays allow discrimination of competitive, non-competitive and un-competitive inhibitors. The majority of inhibitors are competitive (acting at the enzyme's ligand recognition site), non-competitive (acting at a distinct site; potentially interfering with co-factor or co-enzyme binding) or of mixed type. One rare example of an uncompetitive inhibitor is lithium ions, which are effective inhibitors at inositol monophosphatase only in the presence of high substrate concentrations. Some inhibitors are irreversible, including a group known as suicide substrates, which bind to the ligand recognition site and then couple covalently to the enzyme. It is beyond the scope of the Concise Guide To PHARMACOLOGY 2013/14 to give mechanistic

information about the inhibitors described, although generally this information is available from the indicated literature.

Many enzymes require additional entities for functional activity. Some of these are used in the catalytic steps, while others promote a particular conformational change. Co-factors are tightly bound to the enzyme and include metal ions and heme groups. Co-enzymes are typically small molecules which accept or donate functional groups to assist in the enzymatic reaction. Examples include ATP, NAD, NADP and S-adenosylmethionine, as well as a number of vitamins, such as riboflavin (vitamin B1) and thiamine (vitamin B2). Where co-factors/co-enzymes have been identified, the Guide indicates their involvement.

Acknowledgements

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Conflict of interest

The authors state that there is no conflict of interest to disclose.

Further reading

http://www.chem.qmul.ac.uk/iubmb/

List of records presented

Acetylcholine turnover

Overview: Acetylcholine is familiar as a neurotransmitter in the central nervous system and in the periphery. In the somatic nervous system, it activates nicotinic acetylcholine receptors at the skeletal neuromuscular junction. It is also employed in the autonomic nervous system, in both parasympathetic and sympathetic branches; in the former, at the smooth muscle neuromuscular junction, activating muscarinic acetylcholine receptors. In the latter, acetylcholine is involved as a neurotransmitter at the ganglion, activating nicotinic acetylcholine receptors. Acetylcholine is synthesised in neurones through the action of choline O-acetyltransferase and metabolised after release through the extracellular action of acetylcholinesterase and cholinesterase. Choline is accumulated from the extracellular medium by selective transporters (see SLC5A7 and the SLC44 family). Acetylcholine is accumulated in synaptic vesicles through the action of the vesicular acetylcholine transporter SLC18A3.

Nomenclature	Common abbreviation	HGNC, UniProt	EC number: reaction	Comment
choline O-acetyltransferase	ChAT	*CHAT*, P28329	2.3.1.6: acetyl CoA + choline = acetylcholine + coenzyme A	Splice variants of choline O-acetyltransferase are suggested to be differentially distributed in the periphery and CNS (see [3])

Nomenclature	acetylcholinesterase	butyrylcholinesterase
Common abbreviation	AChE	BChE
HGNC, UniProt	*ACHE*, P22303	*BCHE*, P06276
EC number	3.1.1.7: acetylcholine + H_2O = acetic acid + choline + H^+	3.1.1.7: acetylcholine + H_2O = acetic acid + choline + H^+
(Sub)family-selective inhibitors (pIC_{50})	physostigmine (7.6 – 7.8) [6]	physostigmine (7.6 – 7.8) [6]
Selective inhibitors (pIC_{50})	donepezil (7.7 – 8.1) [4,6], BW284C51 (7.7) [5]	bambuterol (8.5) [5], rivastigmine (7.4) [6]

Comments: A number of organophosphorus compounds inhibit acetylcholinesterase and cholinesterase irreversibly, including pesticides such as chlorpyrifos-oxon, and nerve agents such as tabun, soman and sarin. AChE is unusual in its exceptionally high turnover rate which has been calculated at 740 000/min/molecule [7].

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Adenosine turnover

Overview: A multifunctional, ubiquitous molecule, adenosine acts at cell-surface G protein-coupled receptors, as well as numerous enzymes, including protein kinases and adenylyl cyclase. Extracellular adenosine is thought to be produced either by export or by metabolism, predominantly through ecto-5′-nucleotidase activity (also producing inorganic PO_3^{4-}). It is inactivated either by extracellular metabolism *via* adenosine deaminase (also producing NH_3) or, following uptake by nucleoside transporters, *via* adenosine deaminase or adenosine kinase (requiring ATP as co-substrate). Intracellular adenosine may be produced by cytosolic 5′-nucleotidases or through S-adenosylhomocysteine hydrolase (also producing L-homocysteine).

Nomenclature	Adenosine deaminase	Adenosine kinase	Ecto-5′-Nucleotidase	S-Adenosylhomocysteine hydrolase
Common abbreviation	ADA	ADK	NT5E	SAHH
HGNC, UniProt	*ADA*, P00813	*ADK*, P55263	*NT5E*, P21589	*AHCY*, P23526
EC number	3.5.4.4	2.7.1.20	3.1.3.5	3.3.1.1
Rank order of affinity	2′-deoxyadenosine > adenosine	adenosine	AMP, 5′-GMP, 5′-IMP, 5′-UMP > 5′-dAMP, 5′-dGMP	S-adenosylhomocysteine
Products	2′-deoxyinosine, inosine	AMP	adenosine, guanine, inosine, uridine	adenosine
Selective inhibitors (pIC_{50})	EHNA (pK_i 8.8) [8], pentostatin (10.8) [8]	A134974 (10.2) [14], ABT702 (8.8) [11]	αβ-methyleneADP (8.7) [9]	3-deazaadenosine (8.5) [10]

Nomenclature	5′-nucleotidase IA	5′-nucleotidase IB	5′-nucleotidase II	5′-nucleotidase III	Mitochondrial 5′-nucleotidase
HGNC, UniProt	*NT5C1A*, Q9BXI3	*NT5C1B*, Q96P26	*NT5C2*, P49902	*NT5C3A*, Q9H0P0	*NT5M*, Q9NPB1
EC number	3.1.3.5	3.1.3.5	3.1.3.5	3.1.3.5	3.1.3.-

Comments: With the exception of mitochondrial 5′-nucleotidase, each of the 5′-nucleotidases are localised to the cytoplasm.

An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, *CECR1*, Q9NZK5) has been identified [13], which is insensitive to EHNA [15]. Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: *ADAT1* (Q9BUB4) deaminates transfer RNA; *ADAR* (EC 3.5.4.-, also known as 136 kDa double-stranded RNA-binding protein, P136, K88DSRBP, Interferon-inducible protein 4); *ADARB1* (EC 3.5.-.-, also known as dsRNA adenosine deaminase) and *ADARB2* (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, *DPP4*, also known as T-cell activation antigen CD26, TP103, adenosine deaminase complexing protein 2) to form a cell-surface activity [12].

Further reading

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Amino acid hydroxylases

Overview: The amino acid hydroxylases (monooxygenases), E.C.1.14.16.-, are iron-containing enzymes which utilise molecular oxygen and tetrahydrobiopterin as co-substrate and co-factor, respectively. In humans, as well as in other mammals, there are two distinct L-tryptophan hydroxylase 2 genes. In humans, these genes are located on chromosomes 11 and 12 and encode two different homologous enzymes, TPH1 and TPH2.

Nomenclature	L-Phenylalanine hydroxylase	L-Tyrosine hydroxylase	L-Tryptophan hydroxylase 1	L-Tryptophan hydroxylase 2
Common abbreviation	PH	TH	TPH	TPH
HGNC, UniProt	*PAH*, P00439	*TH*, P07101	*TPH1*, P17752	*TPH2*, Q8IWU9
EC number	1.14.16.1: L-phenylalanine + O_2 -> L-tyrosine	1.14.16.2: L-tyrosine + O_2 -> L-DOPA	1.14.16.4	1.14.16.4
Endogenous activator (Rat)	Protein kinase A-mediated phosphorylation [16]	Protein kinase A-mediated phosphorylation [19]	Protein kinase A-mediated phosphorylation [20]	Protein kinase A-mediated phosphorylation [20]
Endogenous substrates	L-phenylalanine	L-tyrosine	L-tryptophan	L-tryptophan
Products	L-tyrosine	L-DOPA	5-hydroxy-L-tryptophan	5-hydroxy-L-tryptophan
Cofactors	tetrahydrobiopterin	Fe^{2+}, tetrahydrobiopterin	–	–
Selective inhibitors (pIC_{50})	α-methylphenylalanine [18], PCPA	–	6-fluorotryptophan [21], α-propyldopacetamide, fenfluramine, PCPA	6-fluorotryptophan [21], α-propyldopacetamide, fenfluramine, PCPA
Inhibitors (pIC_{50})	–	3-chlorotyrosine, 3-iodotyrosine, α-methyltyrosine, α-propyldopacetamide	–	–
Comment	PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monooxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria	TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [17]	–	–

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L-Arginine turnover

Overview: L-arginine is a basic amino acid with a guanidino sidechain. As an amino acid, metabolism of L-arginine to form L-ornithine, catalysed by arginase, forms the last step of the urea production cycle. L-Ornithine may be utilised as a precursor of polyamines (see Carboxylases and Decarboxylases) or recycled via L-argininosuccinic acid to L-arginine. L-Arginine may itself be decarboxylated to form agmatine, although the prominence of this pathway in human tissues is uncertain. L-Arginine may be used as a precursor for guanidoacetic acid formation in the creatine synthesis pathway under the influence of arginine:glycine amidinotransferase with L-ornithine as a byproduct. Nitric oxide synthase uses L-arginine to generate NO, with L-citrulline also as a byproduct. L-Arginine in proteins may be subject to post-translational modification through methylation, catalysed by protein arginine methyltransferases. Subsequent proteolysis can liberate asymmetric N^G,N^G-dimethyl-L-arginine (ADMA), which is an endogenous inhibitor of nitric oxide synthase activities. ADMA is hydrolysed by dimethylarginine dimethylhydrolase activities to generate L-citrulline and dimethylamine.

Arginase

Overview: Arginase (EC 3.5.3.1) are manganese-containing isoforms, which appear to show differential distribution, where the ARG1 isoform predominates in the liver and erythrocytes, while ARG2 is associated more with the kidney.

Nomenclature	Arginase I	Arginase II
Common abbreviation	ARG1	ARG2
HGNC, UniProt	*ARG1*, P05089	*ARG2*, P78540

Comments: N^{ω}-hydroxyarginine, an intermediate in NOS metabolism of L-arginine acts as a weak inhibitor and may function as a physiological regulator of arginase activity. Although isoform-selective inhibitors of arginase are not available, examples of inhibitors selective for arginase compared to NOS are N^{ω}-hydroxy-nor-L-arginine [34], S-(2-boronoethyl)-L-cysteine [25,30] and 2(S)-amino-6-boronohexanoic acid [23,25].

Arginine: glycine amidinotransferase

Nomenclature	Arginine:glycine amidinotransferase
Common abbreviation	AGAT
HGNC, UniProt	*GATM*, P50440
EC number	2.1.4.1

Dimethylarginine dimethylaminohydrolases

Overview: Dimethylarginine dimethylaminohydrolases (DDAH, EC 3.5.3.18) are cytoplasmic enzymes which hydrolyse N^G,N^G-dimethyl-L-arginine to form dimethylamine and L-citrulline.

Nomenclature	N^G,N^G-Dimethylarginine dimethylaminohydrolase 1	N^G,N^G-Dimethylarginine dimethylaminohydrolase 2
Common abbreviation	DDAH1	DDAH2
HGNC, UniProt	*DDAH1*, O94760	*DDAH2*, O95865
Cofactors	Zn^{2+}	–

Nitric oxide synthases

Overview: Nitric oxide synthases (NOS, E.C. 1.14.13.39) utilise L-arginine (not D-arginine) and molecular oxygen to generate NO and L-citrulline. The nomenclature suggested by **NC-IUPHAR** of NOS I, II and III [32] has not gained wide acceptance. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for Ca^{2+}/calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158) 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
Common abbreviation	eNOS	iNOS	nNOS
HGNC, UniProt	*NOS3*, P29474	*NOS2*, P35228	*NOS1*, P29475
Selective inhibitors (pIC_{50})	–	aminoguanidine [26], 1400W (8.2) [28], 2-amino-4-methylpyridine (7.4) [27], PIBTU (7.3) [29], NIL (5.5) [33]	N^{ω}propyl-L-arginine (pK_i 7.2 - Rat) [35], 3-bromo-7NI (6.1 – 6.5) [24], 7NI (5.3) [22]

Comments: The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes [31]. NADPH:O_2 oxidoreductase catalyses the formation of superoxide anion/H_2O_2 in the absence of L-arginine and tetrahydrobiopterin.

Protein arginine N-methyltransferases

Overview: Protein arginine N-methyltransferases (PRMT, EC 2.1.1.-) encompass histone arginine *N*-methyltransferases (PRMT4, PRMT7, EC 2.1.1.125) and myelin basic protein *N*-methyltransferases (PRMT7, EC 2.1.1.126). They are dimeric or tetrameric enzymes which use S-adenosyl methionine as a methyl donor, generating S-adenosyl-L-homocysteine as a by-product. They generate both mono-methylated and di-methylated products; these may be symmetric (SDMA) or asymmetric (N^G,N^G-dimethyl-L-arginine) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

Nomenclature	PRMT1	PRMT2	PRMT3	PRMT4	PRMT5	PRMT6	PRMT7	PRMT8	PRMT9	PRMT10
HGNC, UniProt	*PRMT1*, Q99873	*PRMT2*, P55345	*PRMT3*, O60678	*CARM1*, Q86X55	*PRMT5*, O14744	*PRMT6*, Q96LA8	*PRMT7*, Q9NVM4	*PRMT8*, Q9NR22	*FBXO11*, Q86XK2	*PRMT10*, Q6P2P2
EC number	–	–	–	2.1.1.125	–	–	2.1.1.125, 2.1.1.126	–	–	–

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Carboxylases and decarboxylases

Carboxylases

Overview: The carboxylases allow the production of new carbon-carbon bonds by introducing HCO_3^- or CO_2 into target molecules. Two groups of carboxylase activities, some of which are bidirectional, can be defined on the basis of the cofactor requirement, making use of biotin (EC 6.4.1.-) or vitamin K hydroquinone (EC 4.1.1.-).

Nomenclature	Pyruvate carboxylase	Acetyl-CoA carboxylase 1	Acetyl-CoA carboxylase 2	Propionyl-CoA carboxylase	γ-Glutamyl carboxylase
Common abbreviation	PC	ACC1	ACC2	–	GGCX
HGNC, UniProt	*PC*, P11498	*ACACA*, Q13085	*ACACB*, O00763	–	*GGCX*, P38435
Subunits	–	–	–	Propionyl-CoA carboxylase α subunit, Propionyl-CoA carboxylase β subunit	–
EC number	6.4.1.1	6.4.1.2	6.4.1.2	6.4.1.3	4.1.1.90
Endogenous substrates	ATP, pyruvic acid	ATP, acetyl CoA	ATP, acetyl CoA	ATP, propionyl-CoA	glutamyl peptides
Products	ADP, oxalacetic acid, PO_3^{4-}	malonyl-CoA, ADP, PO_3^{4-}	malonyl-CoA, ADP, PO_3^{4-}	ADP, methylmalonyl-CoA, PO_3^{4-}	carboxyglutamyl peptides
Cofactors	biotin	biotin	biotin	biotin	NADPH, vitamin K hydroquinone
Selective inhibitors (pIC_{50})	–	TOFA [38]	TOFA [38]	–	–
Comment	–	Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase	Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase	Propionyl-CoA carboxylase is able to function in both forward and reverse activity modes, as a ligase (carboxylase) or lyase (decarboxylase), respectively	Loss-of-function mutations in γ-glutamyl carboxylase are associated with clotting disorders

Decarboxylases

Overview: The decarboxylases generate CO_2 and the indicated products from acidic substrates, requiring pyridoxal phosphate or pyruvic acid as a co-factor.

Nomenclature	S-Adenosylmethionine decarboxylase	L-Arginine decarboxylase	L-Aromatic amino-acid decarboxylase	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2
Common abbreviation	SAMDC	ADC	AADC	GAD1	GAD2
HGNC, UniProt	*AMD1*, P17707	*ADC*, Q96A70	*DDC*, P20711	*GAD1*, Q99259	*GAD2*, Q05329
EC number	4.1.1.50	4.1.1.19	4.1.1.28: L-DOPA -> dopamine + CO_2	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2
Endogenous substrates	S-adenosyl methionine	L-arginine	L-tryptophan, L-DOPA, 5-hydroxy-L-tryptophan	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid
Products	5′-deoxyadenosyl-(3-aminopropyl) methylsulfonium	agmatine [43]	5-HT, dopamine	GABA	GABA
Cofactors	pyruvic acid	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate

Nomenclature	S-Adenosylmethionine decarboxylase	L-Arginine decarboxylase	L-Aromatic amino-acid decarboxylase	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2
Selective inhibitors (pIC_{50})	SAM486A (8.0) [41]	–	3-hydroxybenzylhydrazine, benserazide, carbidopa, L-α-methyldopa	s-allylglycine	s-allylglycine
Comment	s-allylglycine is also an inhibitor of SAMDC [39]	The presence of a functional ADC activity in human tissues has been questioned [36]	AADC is a homodimer. Reaction 1: L-DOPA -> dopamine + CO_2, Reaction 2: 5-hydroxy-L-tryptophan -> 5-HT + CO_2, Reaction 3: L-tryptophan -> tryptamine + CO_2	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [42]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading)	

Nomenclature	Histidine decarboxylase	Malonyl-CoA decarboxylase	Ornithine decarboxylase	Phosphatidylserine decarboxylase
Common abbreviation	HDC	MLYCD	ODC	PSDC
HGNC, UniProt	*HDC*, P19113	*MLYCD*, O95822	*ODC1*, P11926	*PISD*, Q9UG56
EC number	4.1.1.22	4.1.1.9	4.1.1.17	4.1.1.65
Endogenous substrates	L-histidine	malonyl-CoA	L-ornithine	phosphatidylserine
Products	histamine	acetyl CoA	putrescine	phosphatidylethanolamine
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	pyruvic acid
Selective inhibitors (pIC_{50})	AMA, FMH [37]	–	APA, DFMO	–
Comment	–	Inhibited by AMP-activated protein kinase-evoked phosphorylation [40]	The activity of ODC is regulated by the presence of an antizyme (ENSG00000104904) and an ODC antizyme inhibitor (ENSG00000155096)	S-allylglycine is also an inhibitor of SAMDC [39]

Further reading

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Catecholamine turnover

Overview: Catecholamines are defined by the presence of two adjacent hydroxyls on a benzene ring with a sidechain containing an amine. The predominant catacholamines in mammalian biology are the neurotransmitter/hormones dopamine, (-)-noradrenaline (norepinephrine) and (-)-adrenaline (epinephrine). These hormone/transmitters are synthesized by sequential metabolism from L-phenylalanine via L-tyrosine. Hydroxylation of L-tyrosine generates L-DOPA, which is decarboxylated to form dopamine. Hydroxylation of the ethylamine sidechain generates (-)-noradrenaline (norepinephrine), which can be methylated to form (-)-adrenaline (epinephrine). In particular neuronal and adrenal chromaffin cells, the catecholamines dopamine, (-)-noradrenaline and (-)-adrenaline are accumulated into vesicles under the influence of the vesicular monoamine transporters (VMAT1/SLC18A1 and VMAT2/SLC18A2). After release into the synapse or the bloodstream, catecholamines are accumulated through the action cell-surface transporters, primarily the dopamine (DAT/SLC6A3) and norepinephrine transporter (NET/SLC6A2). The primary routes of metabolism of these catecholamines are oxidation via monoamine oxidase activities of methylation via catechol O-methyltransferase.

Nomenclature	Common abbreviation	HGNC, UniProt	EC number	Endogenous activator (Rat)	Endogenous substrates	Products	Cofactors	Selective inhibitors (pIC_{50})	Comment
L-Phenylalanine hydroxylase	PH	*PAH*, P00439	1.14.16.1: L-phenylalanine + O_2 -> L-tyrosine	Protein kinase A-mediated phosphorylation [44]	L-phenylalanine	L-tyrosine	tetrahydrobiopterin	α-methylphenylalanine [49], PCPA	PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monooxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria

Nomenclature	Common abbreviation	HGNC, UniProt	EC number	Cofactors	Comment
Tyrosine aminotransferase	TAT	*TAT*, P17735	2.6.1.5: L-tyrosine + α-ketoglutaric acid -> 4-hydroxyphenylpyruvic acid + L-glutamic acid	pyridoxal phosphate	Tyrosine may also be metabolized in the liver by tyrosine transaminase to generate 4-hydroxyphenylpyruvic acid, which can be further metabolized to homogentisic acid., TAT is a homodimer, where loss-of-function mutations are associated with type II tyrosinemia

Nomenclature	Common abbreviation	HGNC, UniProt	EC number	Endogenous substrates	Products	Cofactors	Selective inhibitors (pIC_{50})	Comment
L-Aromatic amino-acid decarboxylase	AADC	*DDC*, P20711	4.1.1.28: L-DOPA -> dopamine + CO_2	L-tryptophan, L-DOPA, 5-hydroxy-L-tryptophan	5-HT, dopamine	pyridoxal phosphate	3-hydroxybenzylhydrazine, benserazide, carbidopa, L-α-methyldopa	AADC is a homodimer, Reaction 1: L-DOPA -> dopamine + CO_2, Reaction 2: 5-hydroxy-L-tryptophan -> 5-HT + CO_2, Reaction 3: L-tryptophan -> tryptamine + CO_2

Nomenclature	Common abbreviation	HGNC, UniProt	EC number	Endogenous activators	Endogenous substrates	Products	Cofactors	Inhibitors (pIC_{50})	Comment
L-Tyrosine hydroxylase	TH	*TH*, P07101	1.14.16.2: L-tyrosine + O_2 -> L-DOPA	Protein kinase A-mediated phosphorylation [51]	L-tyrosine	L-DOPA	Fe^{2+}, tetrahydrobiopterin	3-chlorotyrosine, 3-iodotyrosine, α-methyltyrosine, α-propyldopacetamide	TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [47]

Nomenclature	Common abbreviation	HGNC, UniProt	EC number	Cofactors	Selective inhibitors (pIC_{50})	Comment
Dopamine beta-hydroxylase (dopamine beta-monooxygenase)	DBH	*DBH*, P09172	1.14.17.1: dopamine + O_2 -> (-)-noradrenaline + H_2O	Cu^{2+}, L-ascorbic acid	nepicastat (8.0) [55]	DBH is a homotetramer. A protein structurally-related to DBH (*MOXD1*, Q6UVY6) has been described and for which a function has yet to be identified [45]

Nomenclature	Common abbreviation	HGNC, UniProt	EC number	Cofactors	Selective inhibitors (pIC_{50})
Phenylethanolamine N-methyltransferase	PNMT	*PNMT*, P11086	2.1.1.28: (-)-noradrenaline -> (-)-adrenaline	S-adenosyl methionine	LY134046 (pK_i 7.6) [48]

Nomenclature	Monoamine oxidase A	Monoamine oxidase B
Common abbreviation	MAO-A	MAO-B
HGNC, UniProt	*MAOA*, P21397	*MAOB*, P27338
EC number	1.4.3.4: dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH_3	1.4.3.4: dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH_3
Cofactors	flavin adenine dinucleotide	flavin adenine dinucleotide
Selective inhibitors (pIC_{50})	befloxatone [46], clorgyline, pirlindole [53]	lazabemide [50], L-Deprenyl, rasagiline [56]
Comment	Reaction 1: dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH_3, Reaction 2: (-)-noradrenaline -> 3,4-dihydroxymandelic acid + NH_3, Reaction 3: (-)-adrenaline -> 3,4-dihydroxymandelic acid + NH_3, Reaction 4: 5-HT -> 5-hydroxyindole acetaldehyde + NH_3, Reaction 5: tyramine -> 4-hydroxyphenyl acetaldehyde + NH_3	–

Nomenclature	Common abbreviation	HGNC, UniProt	EC number	Cofactors	Selective inhibitors (pIC_{50})	Comment
Catechol-O-methyltransferase	COMT	*COMT*, P21964	2.1.1.6: dopamine -> 3-methoxytyramine	S-adenosyl methionine	entacapone [52,54], tolcapone [52,54]	COMT appears to exist in both membrane-bound and soluble forms. COMT has also been described to methylate steroids, particularly hydroxyestradiols, Reaction 1: dopamine -> 3-methoxytyramine, Reaction 2: (-)-noradrenaline -> normetanephrine, Reaction 3: (-)-adrenaline -> metanephrine, Reaction 4: 3,4-dihydroxymandelic acid -> vanillylmandelic acid

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Ceramide turnover

Overview: Ceramides are a family of sphingophospholipids synthesized in the endoplasmic reticulum, which mediate cell stress responses, including apoptosis, autophagy and senescence, Serine palmitoyltransferase generates 3-Ketosphinganine, which is reduced to sphinganine (dihydrosphingosine). N-Acylation allows the formation of dihydroceramides, which are subsequently reduced to form ceramides. Once synthesized, ceramides are trafficked from the ER to the Golgi bound to the ceramide transfer protein, CERT (*COL4A3BP*, Q9Y5P4). Ceramide can be metabolized via multiple routes, ensuring tight regulation of its cellular levels. Addition of phosphocholine generates sphingomyelin while carbohydrate is added to form glucosyl- or galactosylceramides. Ceramidase re-forms sphingosine or sphinganine from ceramide or dihydroceramide. Phosphorylation of ceramide generates ceramide phosphate. The determination of accurate kinetic parameters for many of the enzymes in the sphingolipid metabolic pathway is complicated by the lipophilic nature of the substrates.

Serine palmitoyltransferase

Overview: The functional enzyme is a heterodimer of SPT1 (LCB1) with either SPT2 (LCB2) or SPT3 (LCB2B); the small subunits of SPT (ssSPTa or ssSPTb) bind to the heterodimer to enhance enzymatic activity. The complexes of SPT1/SPT2/ssSPTa and SPT1/SPT2/ssSPTb were most active with palmitoylCoA as substrate, with the latter complex also showing some activity with stearoylCoA [62]. Complexes involving SPT3 appeared more broad in substrate selectivity, with incorporation of myristoylCoA prominent for SPT1/SPT3/ssSPTa complexes, while SP1/SPT3/ssSPTb complexes had similar activity with C16, C18 and C20 acylCoAs [62].

Nomenclature	serine palmitoyltransferase, long chain base subunit 1	serine palmitoyltransferase, long chain base subunit 2	serine palmitoyltransferase, long chain base subunit 3	serine palmitoyltransferase, small subunit A	serine palmitoyltransferase, small subunit B
Common abbreviation	SPT1	SPT2	SPT3	SPTSSA	SPTSSB
HGNC, UniProt	*SPTLC1*, O15269	*SPTLC2*, O15270	*SPTLC3*, Q9NUV7	*SPTSSA*, Q969W0	*SPTSSB*, Q8NFR3
EC number	2.3.1.50: palmitoylCoA + L-serine -> 3-Ketosphinganine + coenzyme A + CO_2			–	–
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	–	–
Selective inhibitors (pIC_{50})	myriocin [67]	myriocin [67]	myriocin [67]	–	–

3-ketodihydrosphingosine reductase

Nomenclature	HGNC, UniProt	EC number	Cofactors
3-ketodihydrosphingosine reductase	*KDSR*, Q06136	1.1.1.102: 3-Ketosphinganine + NADPH -> sphinganine + NADP+	NADPH

Ceramide synthase

Overview: This family of enzymes, also known as sphingosine *N*-acyltransferase, is located in the ER facing the cytosol with an as-yet undefined topology and stoichiometry. Ceramide synthase *in vitro* is sensitive to inhibition by the fungal derived toxin, fumonisin B1.

Nomenclature	ceramide synthase 1	ceramide synthase 2	ceramide synthase 3
Common abbreviation	CERS1	CERS2	CERS3
HGNC, UniProt	*CERS1*, P27544	*CERS2*, Q96G23	*CERS3*, Q8IU89
EC number	2.3.1.24: sphinganine + acylCoA -> dihydroceramide + coenzyme A, sphingosine + acylCoA -> ceramide + coenzyme A		
Substrates	C18-CoA [76]	C24- and C26-CoA [65]	C26-CoA and longer [69,71]

Nomenclature	ceramide synthase 4	ceramide synthase 5	ceramide synthase 6
Common abbreviation	CERS4	CERS5	CERS6
HGNC, UniProt	*CERS4*, Q9HA82	*CERS5*, Q8N5B7	*CERS6*, Q6ZMG9
EC number	2.3.1.24: sphinganine + acylCoA -> dihydroceramide + coenzyme A, sphingosine + acylCoA -> ceramide + coenzyme A		
Substrates	C18-, C20- and C22-CoA [72]	C16-CoA [64,72]	C14- and C16-CoA [68]

Sphingolipid Δ^4-desaturase

Overview: DEGS1 and DEGS2 are 4TM membrane proteins.

Nomenclature	delta(4)-desaturase, sphingolipid 1	delta(4)-desaturase, sphingolipid 2
HGNC, UniProt	*DEGS1*, O15121	*DEGS2*, Q6QHC5
EC number	1.14.-.-: dihydroceramide + NADH + O_2 -> ceramide + H_2O + NAD, sphinganine + NADH + O_2 -> sphingosine + H_2O + NAD	
Cofactors	NAD	NAD
Comment	Myristoylation of DEGS1 enhances its activity and targets it to the mitochondria [59]	–

Comments: DEGS1 activity is inhibited by a number of natural products, including curcumin and Δ^9-tetrahydrocannabinol [60].

Sphingomyelin synthase

Overview: Following translocation from the ER to the Golgi under the influence of the ceramide transfer protein, sphingomyelin synthases allow the formation of sphingomyelin by the transfer of phosphocholine from the phospholipid phosphatidylcholine.

Sphingomyelin synthase-related protein 1 is structurally related but lacks sphingomyelin synthase activity.

Nomenclature	sphingomyelin synthase 1	sphingomyelin synthase 2
HGNC, UniProt	*SGMS1*, Q86VZ5	*SGMS2*, Q8NHU3
EC number	2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol	
Comment	–	Palmitoylation of sphingomyelin synthase 2 may allow targeting to the plasma membrane [75]

Nomenclature	HGNC, UniProt	EC number
sterile alpha motif domain containing 8	*SAMD8*, Q96LT4	2.7.8.-: ceramide + phosphatidylethanolamine -> ceramide phosphoethanolamine

Sphingomyelin phosphodiesterase

Overview: Also known as sphingomyelinase.

Nomenclature	sphingomyelin phosphodiesterase 1, acid lysosomal	sphingomyelin phosphodiesterase 2, neutral membrane (neutral sphingomyelinase)	sphingomyelin phosphodiesterase 3, neutral membrane (neutral sphingomyelinase II)	sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3)
HGNC, UniProt	*SMPD1*, P17405	*SMPD2*, O60906	*SMPD3*, Q9NY59	*SMPD4*, Q9NXE4
EC number	3.1.4.12: sphingomyelin -> ceramide + phosphocholine			

Nomenclature	sphingomyelin phosphodiesterase, acid-like 3A	sphingomyelin phosphodiesterase, acid-like 3B
HGNC, UniProt	*SMPDL3A*, Q92484	*SMPDL3B*, Q92485
EC number	3.1.4.-: sphingomyelin -> ceramide + phosphocholine	

Neutral sphingomyelinase coupling factors

Overview: Protein FAN [58] and polycomb protein EED [70] allow coupling between TNF receptors and neutral sphingomyelinase phosphodiesterases.

Nomenclature	embryonic ectoderm development	neutral sphingomyelinase (N-SMase) activation associated factor
HGNC, UniProt	*EED*, O75530	*NSMAF*, Q92636

Ceramide glucosyltransferase

Nomenclature	HGNC, UniProt	EC number	Selective inhibitors	Comment
UDP-glucose ceramide glucosyltransferase	*UGCG*, Q16739	2.4.1.80: UDP-glucose + ceramide = UDP + glucosylceramide	miglustat [57]	Glycoceramides are an extended family of sphingolipids, differing in the content and organization of the sugar moieties, as well as the acyl sidechains

Acid ceramidase

Overview: The five human ceramidases may be divided on the basis of pH optimae into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	HGNC, UniProt	EC number	Comment
N-acylsphingosine amidohydrolase (acid ceramidase) 1	*ASAH1*, Q13510	3.5.1.23: ceramide -> sphingosine + a fatty acid	This lysosomal enzyme is proteolysed to form the mature protein made up of two chains from the same gene product [63]

Neutral ceramidases

Overview: The five human ceramidases may be divided on the basis of pH optimae into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2B	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2C
HGNC, UniProt	*ASAH2*, Q9NR71	*ASAH2B*, P0C7U1	*ASAH2C*, P0C7U2
EC number	3.5.1.23: ceramide -> sphingosine + a fatty acid	–	–
Comment	The enzyme is associated with the plasma membrane [74]	–	–

Comments: Two further structurally-related proteins have been identified (*ASAH2B*, P0C7U1 and *ASAH2C*, P0C7U2). ASAH2B appears to be an enzymatically inactive protein, which may result from gene duplication and truncation.

Alkaline ceramidases

Overview: The five human ceramidases may be divided on the basis of pH optimae into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	alkaline ceramidase 1	alkaline ceramidase 2	alkaline ceramidase 3
HGNC, UniProt	*ACER1*, Q8TDN7	*ACER2*, Q5QJU3	*ACER3*, Q9NUN7
EC number	3.5.1.23: ceramide -> sphingosine + a fatty acid	3.5.1.23: ceramide -> sphingosine + a fatty acid	3.5.1.-
Comment	ACER1 is associated with the ER [73]	ACER2 is associated with the Golgi apparatus [77]	ACER3 is associated with the ER and Golgi apparatus [66]

Ceramide kinase

Nomenclature	HGNC, UniProt	EC number	Selective inhibitors (pIC_{50})
ceramide kinase	*CERK*, Q8TCT0	2.7.1.138: ceramide + ATP -> ceramide 1-phosphate + ADP	NVP 231 (7.9) [61]

Comments: A ceramide kinase-like protein has been identified in the human genome (*CERKL*, Q49MI3).

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Cyclic nucleotide turnover

Overview: Cyclic nucleotides are second messengers generated by cyclase enzymes from precursor triphosphates and hydrolysed by phosphodiesterases. The cellular actions of these cyclic nucleotides are mediated through activation of protein kinases (cAMP- and cGMP-dependent protein kinases), ion channels (cyclic nucleotide-gated, CNG, and hyperpolarization and cyclic nucleotide-gated, HCN) and guanine nucleotide exchange factors (GEFs, Epac).

Adenylyl cyclases

Overview: Adenylyl cyclase (ENSF00000000188), E.C. 4.6.1.1, converts ATP to cAMP and diphosphate ion. Mammalian membrane-bound adenylyl cyclases are typically made up of two clusters of six TM domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators forskolin, NKH477 (except AC9, [121]) and $G\alpha_s$ (the stimulatory G protein α subunit). adenosine and its derivatives (*e.g.* 2′,5′-dideoxyadenosine), acting through the P-site, appear to be physiological inhibitors of adenylyl cyclase activity [135]. Three families of adenylyl cyclase are distinguishable: calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158)-stimulated (AC1, AC3 and AC8), Ca^{2+}-inhibitable (AC5, AC6 and AC9) and Ca^{2+}-insensitive (AC2, AC4 and AC7) forms.

Calmodulin-stimulated adenylyl cyclases

Nomenclature	AC1	AC3	AC8
HGNC, UniProt	*ADCY1*, Q08828	*ADCY3*, O60266	*ADCY8*, P40145
Endogenous activators	calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158), PKC-evoked phosphorylation [110,132]	calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158), PKC-evoked phosphorylation [88,110]	–
Endogenous inhibitors	$G\alpha_i$, $G\alpha_o$, Gβγ [133–134]	$G\alpha_i$, RGS2 (*RGS2*, P41220), CaM kinase II-evoked phosphorylation [127,134,140]	Ca^{2+} [82]

Calcium-inhibitable adenylyl cyclases

Nomenclature	AC5	AC6	AC9
HGNC, UniProt	*ADCY5*, O95622	*ADCY6*, O43306	*ADCY9*, O60503
Endogenous activators	PKC-evoked phophorylation [111]	–	–
Endogenous inhibitors	$G\alpha_i$, Ca^{2+}, PKA-evoked phosphorylation [108–109,134]	$G\alpha_i$, Ca^{2+}, PKA-evoked phosphorylation, PKC-evoked phosphorylation [87,112,134,141]	Ca^{2+}/calcineurin [120]
Selective inhibitors (pIC_{50})	NKY80 [119]	–	–

Calcium-independent adenylyl cyclases

Nomenclature	AC2	AC4	AC7
HGNC, UniProt	*ADCY2*, Q08462	*ADCY4*, Q8NFM4	*ADCY7*, P51828
Endogenous activators	Gβγ, PKC-evoked phosphorylation [85,114,133]	Gβγ [99]	PKC-evoked phosphorylation [139]
Endogenous inhibitors	–	PKC-evoked phophorylation [143]	–

Comments: NO has been proposed to inhibit AC5 and AC6 selectively [104], although it is unclear whether this phenomenon is of physiological significance. A soluble adenylyl cyclase has been described (*ADCY10*, Q96PN6 [81]), unaffected by either Gα or Gβγ subunits, which has been suggested to be a cytoplasmic bicarbonate (pH-insensitive) sensor [86]. It can be inhibited selectively by KH7 (pIC_{50} 5.0–5.5) [103].

Soluble guanylyl cyclase

Overview: Soluble guanylyl cyclase (GTP diphosphate-lyase (cyclising)), E.C. 4.6.1.2, is a heterodimer comprising α and β chains, both of which have two subtypes in man (predominantly α1β1; [142]). A haem group is associated with the β chain and is the target for the endogenous ligand NO, and, potentially, carbon monoxide [96]. The enzyme converts guanosine-5′-triphosphate (GTP) to the intracellular second messenger 3′,5′-guanosine monophosphate (cGMP).

Nomenclature	Soluble guanylyl cyclase
Common abbreviation	sGC
Subunits	Soluble guanylyl cyclase α 1 subunit, Soluble guanylyl cyclase β 1 subunit
EC number	4.6.1.2
Selective activators	ataciguat [125], BAY412272 [129], cinaciguat [130], NO, riociguat [130], YC1 [96]
Selective inhibitors (pIC_{50})	NS 2028 (8.1 - Bovine) [118], ODQ (7.5) [101]

Comments: ODQ also shows activity at other haem-containing proteins [92], while YC1 may also inhibit cGMP-hydrolysing phosphodiesterases [95,98].

Exchange protein activated by cyclic AMP (Epac)

Overview: Epacs are members of a family of guanine nucleotide exchange factors (ENSFM00250000000899), which also includes *RapGEF5* (GFR, KIAA0277, MR-GEF, Q92565) and *RapGEFL1* (Link-GEFII, Q9UHV5). They are activated endogenously by cAMP and with some pharmacological selectivity by 8-pCPT-2′-O-Me-cAMP [90]. Once activated, Epacs induce an enhanced activity of the monomeric G proteins, Rap1 and Rap2 by facilitating binding of GTP in place of GDP, leading to activation of phospholipase C [126].

Nomenclature	Epac1	Epac2
HGNC, UniProt	*RAPGEF3*, O95398	*RAPGEF4*, Q8WZA2
Selective inhibitors (pIC_{50})	–	HJC 0350 (6.5) [84]

Phosphodiesterases, 3′,5′-cyclic nucleotide

Overview: 3′,5′-Cyclic nucleotide phosphodiesterases (PDEs, 3′,5′-cyclic-nucleotide 5′-nucleotidohydrolase), E.C. 3.1.4.17, catalyse the hydrolysis of a 3′,5′-cyclic nucleotide (usually cAMP or cGMP). 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
HGNC, UniProt	*PDE1A*, P54750	*PDE1B*, Q01064	*PDE1C*, Q14123
Rank order of affinity	cGMP > cAMP	cGMP > cAMP	cGMP = cAMP
Endogenous activators	calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158)	calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158)	calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158)
Selective inhibitors (pIC_{50})	SCH51866 (7.2) [137], vinpocetine (5.1) [113]	SCH51866 (7.2) [137]	SCH51866 (7.2) [137], vinpocetine (4.3) [113]

Comments: PDE1A, 1B and 1C appear to act as soluble homodimers.

Nomenclature	PDE2A	PDE3A	PDE3B
HGNC, UniProt	*PDE2A*, O00408	*PDE3A*, Q14432	*PDE3B*, Q13370
Rank order of affinity	cAMP >> cGMP	–	–
Endogenous activators	cGMP	–	–
Endogenous inhibitors (pIC_{50})	–	cGMP (Selective)	cGMP (Selective)
Selective inhibitors (pIC_{50})	BAY607550 (8.3 – 8.8) [80], EHNA (5.3) [116]	cilostamide (7.5) [131], milrinone (6.3) [131]	cilostamide (7.3) [131], milrinone (6.0) [131]
Comment	EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4)	–	–

Comments: PDE2A is a membrane-bound homodimer. PDE3A and PDE3B are membrane-bound.

Nomenclature	PDE4A	PDE4B	PDE4C	PDE4D
HGNC, UniProt	*PDE4A*, P27815	*PDE4B*, Q07343	*PDE4C*, Q08493	*PDE4D*, Q08499
Activator	–	–	–	PKA-mediated phosphorylation [107]
Rank order of affinity	cAMP >> cGMP	cAMP >> cGMP	cAMP >> cGMP	cAMP >> cGMP
Selective inhibitors (pIC_{50})	rolipram (9.0) [138], YM976 (8.3) [79], RS-25344 (7.2) [123], Ro201724 (6.5) [138]	rolipram (9.0) [138], RS-25344 (6.5) [123], Ro201724 (6.4) [138]	RS-25344 (8.1) [123], rolipram (6.5) [138], Ro201724 (5.4) [138]	RS-25344 (8.4) [123], rolipram (7.2) [138], Ro201724 (6.2) [138]

Comments: 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 [105–106]. PDE4A–D splice variants can be membrane-bound or cytosolic [107]. PDE4 isoforms may be labelled with [^{3}H]rolipram.

Nomenclature	PDE5A
HGNC, UniProt	*PDE5A*, O76074
EC number	3.1.4.17
Activators	Protein kinase A, protein kinase G [89]
Rank order of affinity	cGMP > cAMP
Selective inhibitors (pIC_{50})	T0156 (9.5) [117], sildenafil (9.0) [136], gisadenafil (8.9) [122], SCH51866 (7.2) [137], zaprinast (6.8) [136]

Nomenclature	PDE6A	PDE6B	PDE6C	PDE6D	PDE6G	PDE6H
HGNC, UniProt	*PDE6A*, P16499	*PDE6B*, P35913	*PDE6C*, P51160	*PDE6D*, O43924	*PDE6G*, P18545	*PDE6H*, Q13956

Comments: 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 ($G\alpha_t$) 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	PDE7A	PDE7B	PDE8A	PDE8B
HGNC, UniProt	*PDE7A*, Q13946	*PDE7B*, Q9NP56	*PDE8A*, O60658	*PDE8B*, O95263
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cAMP >> cGMP [115]	cAMP >> cGMP [100]	cAMP >> cGMP [93]	cAMP >> cGMP [102]
Selective inhibitors (pIC_{50})	BRL50481 (6.7 – 6.8) [78,128]	dipyridamole (5.7 – 6.0) [100,124], SCH51866 (5.8) [124], BRL50481 (4.9) [78]	dipyridamole (5.1) [93]	dipyridamole (4.3) [102]
Comment	PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively	–	–	–

Nomenclature	PDE9A	PDE10A	PDE11A
HGNC, UniProt	*PDE9A*, O76083	*PDE10A*, Q9Y233	*PDE11A*, Q9HCR9
EC number	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cGMP >> cAMP [94]	cAMP, cGMP [97]	cAMP, cGMP [91]
Selective inhibitors (pIC_{50})	SCH51866 (5.8) [94], zaprinast (4.5) [94]	–	BC11-38 (6.5) [83]

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Cytochrome P450

Overview: The cytochrome P450 enzyme family (CYP450), E.C. 1.14.-.-, were originally defined by their strong absorbance at 450 nm due to the reduced carbon monoxide-complexed haem component of the cytochromes. They are an extensive family of haem-containing monooxygenases with a huge range of both endogenous and exogenous substrates. Listed below are the human enzymes; their relationship with rodent CYP450 enzyme activities is obscure in that the species orthologue may not mediate metabolism of the same substrates. Although the majority of CYP450 enzyme activities are concentrated in the liver, the extrahepatic enzyme activities also contribute to patho/physiological processes. Genetic variation of CYP450 isoforms is widespread and likely underlies a significant proportion of the individual variation to drug administration.

CYP1 family

Nomenclature	HGNC, UniProt	EC number	Comment
CYP1A1	*CYP1A1*, P04798	1.14.1.1	–
CYP1A2	*CYP1A2*, P05177	1.14.1.1	–
CYP1B1	*CYP1B1*, Q16678	1.14.1.1	Mutations have been associated with primary congenitial glucoma [165]

CYP2 family

Nomenclature	HGNC, UniProt	EC number	Comment
CYP2A6	*CYP2A6*, P11509	1.14.14.1	Metabolises nicotine
CYP2A7	*CYP2A7*, P20853	1.14.14.1	CYP2A7 does not incorporate haem and is functionally inactive [148]
CYP2A13	*CYP2A13*, Q16696	1.14.14.1	–
CYP2B6	*CYP2B6*, P20813	1.14.14.1	–
CYP2C8	*CYP2C8*, P10632	1.14.14.1	Converts arachidonic acid to 11(R)-12(S)-epoxyeicosatrienoic acid or 14(R)-15(S)-epoxyeicosatrienoic acid [168]
CYP2C9	*CYP2C9*, P11712	1.14.13.80, 1.14.13.48, 1.14.13.49	–
CYP2C18	*CYP2C18*, P33260	1.14.14.1	–
CYP2C19	*CYP2C19*, P33261	1.14.13.80, 1.14.13.48, 1.14.13.49	–
CYP2D6	*CYP2D6*, P10635	1.14.14.1	–
CYP2E1	*CYP2E1*, P05181	1.14.14.1	–
CYP2F1	*CYP2F1*, P24903	1.14.14.1	–
CYP2J2	*CYP2J2*, P51589	1.14.14.1	Converts arachidonic acid to 14(R)-15(S)-epoxyeicosatrienoic acid [167]
CYP2R1	*CYP2R1*, Q6VVX0	1.14.13.15	Converts vitamin D_3 to 25-hydroxyvitamin D_3 [146]
CYP2S1	*CYP2S1*, Q96SQ9	1.14.14.1	–

Nomenclature	HGNC, UniProt	EC number	Comment
CYP2U1	*CYP2U1*, Q7Z449	1.14.14.1	–
CYP2W1	*CYP2W1*, Q8TAV3	1.14.14.-	–

Comments: *CYP2A7P1*, *CYP2D7P1*, *CYP2G1P* and AC008537.5-2 (fragment) are uncharacterized potential pseudogenes from the same families.

CYP3 family

Nomenclature	HGNC, UniProt	EC number	Comment
CYP3A4	*CYP3A4*, P08684	1.14.13.67, 1.14.13.97, 1.14.13.32	Metabolises a vast range of xenobiotics, including antidepressants, benzodiazepines, calcium channel blockers, and chemotherapeutic agents
CYP3A5	*CYP3A5*, P20815	1.14.14.1	–
CYP3A7	*CYP3A7*, P24462	1.14.14.1	–
CYP3A43	*CYP3A43*, Q9HB55	1.14.14.1	–

CYP4 family

Nomenclature	HGNC, UniProt	EC number	Comment
CYP4A11	*CYP4A11*, Q02928	1.14.15.3	Converts lauric acid to 12-hydroxylauric acid
CYP4A22	*CYP4A22*, Q5TCH4	1.14.15.3	–
CYP4B1	*CYP4B1*, P13584	1.14.14.1	–
CYP4F2	*CYP4F2*, P78329	1.14.13.30	Responsible for ω-hydroxylation of LTB_4, LXB_4 [155], and tocopherols, including vitamin E [163]
CYP4F3	*CYP4F3*, Q08477	1.14.13.30	Responsible for ω-hydroxylation of LTB_4, LXB_4 [155], and polyunsaturated fatty acids [147,151]
CYP4F8	*CYP4F8*, P98187	1.14.14.1	Converts PGH_2 to 19-hydroxyPGH_2 [145] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [157]
CYP4F11	*CYP4F11*, Q9HBI6	1.14.14.1	–
CYP4F12	*CYP4F12*, Q9HCS2	1.14.14.1	AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12
CYP4F22	*CYP4F22*, Q6NT55	1.14.14.-	Converts arachidonic acid to 16-HETE and 18-HETE [157]
CYP4V2	*CYP4V2*, Q6ZWL3	1.14.-.-	Converts myristic acid to 14-hydroxymyristic acid [156]
CYP4X1	*CYP4X1*, Q8N118	1.14.14.1	Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [164]
CYP4Z1	*CYP4Z1*, Q86W10	1.14.14.1	Converts lauric acid to 12-hydroxylauric acid

CYP5, CYP7 and CYP8 families

Nomenclature	Common name	HGNC, UniProt	EC number	Comment
CYP5A1	–	*TBXAS1*, P24557	5.3.99.5	Converts PGH_2 to thromboxane A_2. Inhibited by dazoxiben [161] and camonagrel [150]
CYP8A1	Prostacyclin synthase	*PTGIS*, Q16647	5.3.99.4	Converts prostaglandin H_2 to prostaglandin I_2 [152]. Inhibited by tranylcypromine [149]
CYP7A1	–	*CYP7A1*, P22680	1.14.13.17	Converts cholesterol to 7α-hydroxycholesterol [158]
CYP7B1	–	*CYP7B1*, O75881	1.14.13.100	Converts DHEA to 7α-DHEA [162]
CYP8B1	–	*CYP8B1*, Q9UNU6	1.14.13.95	Converts 7α-hydroxycholest-4-en-3-one to 7-alpha,12α-dihydroxycholest-4-en-3-one (in rabbit) [153] in the biosynthesis of bile acids

CYP11, CYP17, CYP19, CYP20 and CYP21 families

Nomenclature	Common name	HGNC, UniProt	EC number	Comment
CYP11A1	–	*CYP11A1*, P05108	1.14.15.6	Converts cholesterol to pregnenolone plus 4-methylpentanal
CYP11B1	–	*CYP11B1*, P15538	1.14.15.4	Converts deoxycortisone and 11-deoxycortisol to cortisone and cortisol, respectively Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension Inhibited by metyrapone [166]
CYP11B2	Aldosterone synthase	*CYP11B2*, P19099	1.14.15.4, 1.14.15.5	Converts corticosterone to aldosterone
CYP17A1	–	*CYP17A1*, P05093	1.14.99.9	Converts pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, respectively. Converts 17α-hydroxypregnenolone and 17α-hydroxyprogesterone to dehydroepiandrosterone and androstenedione, respectively Converts corticosterone to cortisol. Inhibited by abiraterone (pIC_{50} 8.4) [160]
CYP19A1	Aromatase	*CYP19A1*, P11511	1.14.14.1	Converts androstenedione and testosterone to estrone and 17β-estradiol, respectively Inhibited by anastrazole [159], and letrozole [144]
CYP20A1	–	*CYP20A1*, Q6UW02	1.14.-.-	–
CYP21A2	–	*CYP21A2*, P08686	1.14.99.10	Converts progesterone and 17α-hydroxyprogesterone to deoxycortisone and 11-deoxycortisol, respectively

CYP24, CYP26 and CYP27 families

Nomenclature	Common name	HGNC, UniProt	EC number	Comment
CYP24A1	–	*CYP24A1*, Q07973	1.14.13.126	Converts 1α,25-dihydroxyvitamin D_3 (calcitriol) to 1α,24R,25-trihydroxyvitamin D_3
CYP26A1	–	*CYP26A1*, O43174	1.14.-.-	Converts retinoic acid to 4-hydroxyretinoic acid. Inhibited by liarozole
CYP26B1	–	*CYP26B1*, Q9NR63	1.14.-.-	Converts retinoic acid to 4-hydroxyretinoic acid
CYP26C1	–	*CYP26C1*, Q6V0L0	1.14.-.-	–
CYP27A1	Sterol 27-hydroxylase	*CYP27A1*, Q02318	1.14.13.15	Converts cholesterol to 27-hydroxyxcholesterol
CYP27B1	–	*CYP27B1*, O15528	1.14.13.13	Converts 25-hydroxyvitamin D_3 to 1α,25-dihydroxyvitamin D_3 (calcitriol)
CYP27C1	–	*CYP27C1*, Q4G0S4	1.14.-.-	–

CYP39, CYP46 and CYP51 families

Nomenclature	Common name	HGNC, UniProt	EC number	Comment
CYP39A1	–	*CYP39A1*, Q9NYL5	1.14.13.99	Converts 24-hydroxycholesterol to 7α,24-dihydroxycholesterol [154]
CYP46A1	Cholesterol 24-hydroxylase	*CYP46A1*, Q9Y6A2	1.14.13.98	Converts cholesterol to 24(S)-hydroxycholesterol
CYP51A1	Lanosterol 14-α-demethylase	*CYP51A1*, Q16850	–	Converts lanosterol to 4,4-dimethylcholesta-8.14.24-trienol

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Eicosanoid turnover

Overview: Eicosanoids are 20-carbon fatty acids, where the usual focus is the polyunsaturated analogue arachidonic acid and its metabolites. Arachidonic acid is thought primarily to derive from phospholipase A2 action on membrane phosphatidylcholine, and may be re-cycled to form phospholipid through conjugation with coenzyme A and subsequently glycerol derivatives. Oxidative metabolism of arachidonic acid is conducted through three major enzymatic routes: cyclooxygenases; lipoxygenases and cytochrome P450-like epoxygenases, particularly CYP2J2. Isoprostanes are structural analogues of the prostanoids (hence the nomenclature D-, E-, F-isoprostanes and isothromboxanes), which are produced in the presence of elevated free radicals in a non-enzymatic manner, leading to suggestions for their use as biomarkers of oxidative stress. Molecular targets for their action have yet to be defined.

Cyclooxygenase

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, indomethacin and paracetamol (acetaminophen). PGH_2 may then be metabolised to prostaglandins and thromboxanes by various prostaglandin synthases in an apparently tissue-dependent manner.

Nomenclature	COX-1	COX-2
HGNC, UniProt	*PTGS1*, P23219	*PTGS2*, P35354
EC number	1.14.99.1	1.14.99.1
Reaction 1:	arachidonic acid => PGG_2 => PGH_2	arachidonic acid => PGG_2 => PGH_2
Reaction 2:	–	docosahexaenoic acid => PGH_3
Selective inhibitors (pIC_{50})	ketorolac (9.72) [190], FR122047 (7.5) [183], flurbiprofen (7.12) [190]	etoricoxib, lumiracoxib, valdecoxib (8.3) [189], rofecoxib (6.1 – 6.5) [190]

Prostaglandin synthases

Overview: Subsequent to the formation of PGH_2, the cytochrome P450 activities thromboxane synthase (CYP5A1, *TBXAS1*, P24557 , EC 5.3.99.5) and prostacyclin synthase (CYP8A1, *PTGIS*, Q16647, EC 5.3.99.4) generate thromboxane A_2 and prostacyclin (PGI_2), respectively. Additionally, multiple enzyme activities are able to generate prostaglandin E_2 (PGE_2), prostaglandin D_2 (PGD_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). PGD_2 can be metabolised to 9α,11β-prostacyclin $F_{2\alpha}$ through the multifunctional enzyme activity of AKR1C3. PGE_2 can be metabolised to 9α,11β-prostacyclin $F_{2\alpha}$ through the 9-ketoreductase activity of CBR1. Conversion of the 15-hydroxyecosanoids, including prostaglandins, lipoxins and leukotrienes to their keto derivatives by the NAD-dependent enzyme HPGD leads to a reduction in their biological activity.

Nomenclature	HGNC, UniProt	EC number	Reaction:	Cofactors	Selective inhibitors (pIC_{50})	Comment
mPGES1	*PTGES*, O14684	5.3.99.3	PGH_2 => PGE_2	glutathione [175]	–	–
mPGES2	*PTGES2*, Q9H7Z7	5.3.99.3	PGH_2 => PGE_2	Thiols, including dihydrolipoic acid [191]	–	–
cPGES	*PTGES3*, Q15185	5.3.99.3	PGH_2 => PGE_2	–	–	Phosphorylated and activated by casein kinase 2 (CK2) [177]. Appears to regulate steroid hormone function by interaction with dimeric hsp90 [170,176].
L-PGDS	*PTGDS*, P41222	5.3.99.2	PGH_2 => PGD_2	–	–	–
H-PGDS	*HPGDS*, O60760	5.3.99.2	PGH_2 => PGD_2	–	HQL-79 (5.3 – 5.5) [169]	–

Nomenclature	AKR1C3	CBR1	HPGD
HGNC, UniProt	*AKR1C3*, P42330	*CBR1*, P16152	*HPGD*, P15428
EC number	1.1.1.188, 1.3.1.20, 1.1.1.213, 1.1.1.63, 1.1.1.64	1.1.1.197, 1.1.1.184, 1.1.1.189	1.1.1.141
Inhibitors	flufenamic acid, indomethacin, flavonoids [182,188]	–	–
Reaction 1:	$PGD_2 + NADP^+ => PGF_{2\alpha} + NADPH + H^+$	$PGE_2 + NADP^+ => PGF_{2\alpha} + NADPH + H^+$	15-hydroxyprostaglandins => 15-ketoprostaglandins
Reaction 2:	–	–	Lipoxin A_4 => 15-keto-lipoxin A_4 [181]
Cofactors	NADP	NADP	–
Comment	Also acts as a hydroxysteroid dehydrogenase activity.	–	–

Comments: YS121 has been reported to inhibit mPGES1 and 5-LOX with a pIC_{50} value of 5.5 [178].

Lipoxygenases

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. For arachidonic acid as substrate, these products are hydroperoxyeicosatetraenoic acids (HPETEs). In humans there are five lipoxygenases, the 5S-(arachidonate : oxygen 5-oxidoreductase), 12R-(arachidonate 12-lipoxygenase, 12R-type), 12S-(arachidonate : oxygen 12-oxidoreductase), and two distinct 15S-(arachidonate : oxygen 15-oxidoreductase) LOXs that oxygenate arachidonic acid in different positions along the carbon chain and form the corresponding 5S-, 12S-, 12R-, or 15S-hydroperoxides, respectively.

Nomenclature	5-LOX	12R-LOX	12S-LOX
HGNC, UniProt	*ALOX5*, P09917	*ALOX12B*, O75342	*ALOX12*, P18054
EC number	1.13.11.34	1.13.11.-	1.13.11.31
Endogenous inhibitor	Protein kinase A-mediated phosphorylation [180]	–	–
Reaction:	arachidonic acid + O_2 => $LTA_4 + H2_2O$	arachidonic acid + O_2 => 12R-HPETE	arachidonic acid + O_2 => 12S-HPETE
Endogenous substrates	arachidonic acid	–	–
Endogenous activators	FLAP (*ALOX5AP*, P20292)	–	–
Selective inhibitors (pIC_{50})	CJ13610 [172], zileuton	–	–
Substrates	–	methyl arachidonate	–
Comment	FLAP activity can be inhibited by MK-886 [171] and BAY-X1005 [174] leading to a selective inhibition of 5-LOX activity	–	–

Nomenclature	15-LOX-1	15-LOX-2	E-LOX
HGNC, UniProt	*ALOX15*, P16050	*ALOX15B*, O15296	*ALOXE3*, Q9BYJ1
EC number	1.13.11.33	1.13.11.33	1.13.11.-
Endogenous substrates	–	–	12R-HPETE
Reaction 1:	arachidonic acid + O_2 => 15S-HPETE	arachidonic acid + O_2 => 15S-HPETE	–
Reaction 2:	linoleic acid + O_2 => 13S-HPODE	–	–
Comment	–	–	E-LOX metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxyalcohol compound [192]

Comments: An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 [173]. Some general LOX inhibitors are NDGA and esculetin. 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 [187].

Leukotriene and lipoxin metabolism

Overview: Leukotriene A_4 (LTA_4), produced by 5-LOX activity, and lipoxins may be subject to further oxidative metabolism; ω-hydroxylation is mediated by CYP4F2 and CYP4F3, while β-oxidation in mitochondria and peroxisomes proceeds in a manner dependent on coenzyme A conjugation. Conjugation of LTA_4 at the 6 position with reduced glutathione to generate LTC_4 occurs under the influence of leukotriene C_4 synthase, with the subsequent formation of LTD_4 and LTE_4, all three of which are agonists at CysLT receptors. LTD_4 formation is catalysed by γ-glutamyltransferase, and subsequently dipeptidase 2 removes the terminal glycine from LTD_4 to generate LTE_4. Leukotriene A4 hydrolase converts the 5,6-epoxide LTA_4 to the 5-hydroxylated LTB_4, an agonist for BLT receptors. LTA_4 is also acted upon by 12S-LOX to produce the trihydroxyeicosatetraenoic acids lipoxins LXA_4 and LXB_4. Treatment with a LTA_4 hydrolase inhibitor in a murine model of allergic airway inflammation increased LXA_4 levels, in addition to reducing LTB_4, in lung lavage fluid [186].

LTA_4 hydrolase is also involved in biosynthesis of resolvin Es. aspirin has been reported to increase endogenous formation of 18S-hydroxyeicosapentaenoate (18S-HEPE) compared with 18R-HEPE, a resolvin precursor. Both enantiomers may be metabolised by human recombinant 5-LOX; recombinant LTA_4 hydrolase converted chiral 5S(6)-epoxide-containing intermediates to resolvin E1 and 18S-resolvin E1 [184].

Nomenclature	Leukotriene C4 synthase	γ-Glutamyltransferase	Dipeptidase 1	Dipeptidase 2	Leukotriene A_4 hydrolase
HGNC, UniProt	*LTC4S*, Q16873	*GGCT*, O75223	*DPEP1*, P16444	*DPEP2*, Q9H4A9	*LTA4H*, P09960
EC number	4.4.1.20	2.3.2.2	3.4.13.19	3.4.13.19	3.3.2.6
Reaction:	LTA_4 +glutathione => LTC_4	$LTC_4 + H_2O$ => LTD_4 + L-glutamate	$LTD_4 + H_2O = LTE_4$ + glycine	$LTD_4 + H_2O = LTE_4$ + glycine	$LTA_4 + H_2O = LTB_4$
Inhibitors	–	–	cilastatin [179]	–	bestatin [185]

Comments: LTA4H is a member of a family of arginyl aminopeptidases (ENSFM00250000001675), which also includes aminopeptidase B (*RNPEP*, 9H4A4) and aminopeptidase B-like 1 (*RNPEPL1*, Q9HAU8). Dipeptidase 1 and 2 are members of a family of membrane dipeptidases (ENSFM00250000001170), which also includes (*DPEP3*, Q9H4B8) for which LTD_4 appears not to be a substrate.

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Endocannabinoid turnover

Overview: The principle endocannabinoids are 2-arachidonoylglycerol (2AG) and anandamide (N-arachidonoylethanolamine, AEA), thought to be generated on demand rather than stored. Mechanisms for release and re-uptake of endocannabinoids (and related entities) are unclear, although candidates for intracellular transport have been suggested. For the generation of 2-arachidonoylglycerol, the key enzyme involved is diacylglycerol lipase (DGL), whilst several routes for anandamide synthesis have been described, the best characterized of which involves *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD, [206]). Inactivation of these endocannabinoids appears to occur predominantly through monoacylglycerol lipase (MGL) and fatty acid amide hydrolase (FAAH) for 2-arachidonoylglycerol and anandamide, respectively. Note that these enzymes also contribute to the turnover of many endogenous ligands inactive at CB1 and CB2 cannabinoid receptors, such as N-oleoylethanolamide, N-palmitoylethanolamine and 2-oleoyl glycerol. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism *via* cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [195,198,207].

Nomenclature	Diacylglycerol lipase α	Diacylglycerol lipase β	*N*-Acylphosphatidylethanolamine-phospholipase D
Common abbreviation	DGLα	DGLβ	NAPE-PLD
HGNC, UniProt	*DAGLA*, Q9Y4D2	*DAGLB*, Q8NCG7	*NAPEPLD*, Q6IQ20
EC number	3.1.1.-	3.1.1.-	–
Selective inhibitors (pIC_{50})	RHC80267, orlistat (7.2) [196]	RHC80267, orlistat (7.0) [196]	–
Comment	–	–	NAPE-PLD activity appears to be enhanced by polyamines in the physiological range [202], but fails to transphosphatidylate with alcohols [205] unlike phosphatidylcholine-specific phospholipase D

Nomenclature	Monoacylglycerol lipase	Fatty acid amide hydrolase	Fatty acid amide hydrolase-2	*N*-Acylethanolamine acid amidase
Common abbreviation	MGL	FAAH	FAAH2	NAAA
HGNC, UniProt	*MGLL*, Q99685	*FAAH*, O00519	*FAAH2*, Q6GMR7	*NAAA*, Q02083
EC number	3.1.1.23	3.5.1.-	3.5.1.-	3.5.1.-
Rank order of affinity	2-oleoyl glycerol = 2-arachidonoylglycerol >> anandamide [199]	anandamide > oleamide > N-oleoylethanolamide > N-palmitoylethanolamine [211]	oleamide > N-oleoylethanolamide > anandamide > N-palmitoylethanolamine [211]	N-palmitoylethanolamine > MEA > SEA ≥ N-oleoylethanolamide > anandamide [210]
Selective inhibitors (pIC_{50})	JZL184 (8.1) [203]	JNJ1661010 (7.8) [200], OL135 (7.4) [211], PF750 (6.3 – 7.8) [193], URB597 (6.3 – 7.0) [211], PF3845 (6.6) [194]	OL135 (7.9) [211], URB597 (7.5 – 8.3) [211]	*S*-OOPP (6.4 - Rat) [208], CCP (5.3) [209]

Comments: Many of the compounds described as inhibitors are irreversible and so potency estimates will vary with incubation time. FAAH2 is not found in rodents [211] and only a few of the inhibitors described have been assessed at this enzyme activity. 2-arachidonoylglycerol has been reported to be hydrolysed by multiple enzyme activities from neural preparations, including *ABHD6* (Q9BV23) [197], *ABHD12* (8N2K0) [197], neuropathy target esterase (*PNPLA6*, Q8IY17 [204]) and carboxylesterase 1 (*CES1*, P23141 [212]). Although these have been incompletely defined, WWL70 has been described to inhibit ABHD6 selectively with a pIC_{50} value of 7.2 [201].

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GABA turnover

Overview: The inhibitory neurotransmitter γ-aminobutyrate (GABA, 4-aminobutyrate) is generated in neurones by glutamic acid decarboxylase. GAD1 and GAD2 are differentially expressed during development, where GAD2 is thought to subserve a trophic role in early life and is distributed throughout the cytoplasm. GAD1 is expressed in later life and is more associated with nerve terminals [213] where GABA is principally accumulated in vesicles through the action of the vesicular inhibitory amino acid transporter SLC32A1. The role of γ-aminobutyraldehyde dehydrogenase (ALDH9A1) in neurotransmitter GABA synthesis is less clear. Following release from neurons, GABA may interact with either $GABA_A$ or $GABA_B$ receptors and may be accumulated in neurones and glia through the action of members of the SLC6 family of transporters. Successive metabolism through GABA transaminase and succinate semialdehyde dehydrogenase generates succinic acid, which may be further metabolized in the mitochondria in the tricarboxylic acid cycle.

Nomenclature	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2
Common abbreviation	GAD1	GAD2
HGNC, UniProt	*GAD1*, Q99259	*GAD2*, Q05329
EC number	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2	
Endogenous substrates	L-glutamic acid, L-aspartic acid	
Products	GABA	
Cofactors	pyridoxal phosphate	
Selective inhibitors (pIC_{50})	s-allylglycine	
Comment	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [215]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading)	

Nomenclature	aldehyde dehydrogenase 9 family, member A1 (γ-aminobutyraldehyde dehydrogenase)
HGNC, UniProt	*ALDH9A1*, P49189
EC number	1.2.1.47: 4-trimethylammoniobutanal + NAD + H_2O = 4-trimethylammoniobutanoate + NADPH + 2 H^+, 1.2.1.3: an aldehyde + H_2O + NAD = a carboxylate + 2 H^+ + NADH, 1.2.1.19: 4-aminobutanal + NAD + H_2O = GABA + NADH + H^+
Cofactors	NAD

Nomenclature	4-aminobutyrate aminotransferase (GABA transaminase)
Common abbreviation	GABA-T
HGNC, UniProt	*ABAT*, P80404
EC number	2.6.1.19: GABA + α-ketoglutaric acid = L-glutamic acid + 4-oxobutanoate, 2.6.1.22: (S)-3-amino-2-methylpropanoate + α-ketoglutaric acid = 2-methyl-3-oxopropanoate + L-glutamic acid
Cofactors	pyridoxal phosphate
Selective inhibitors (pIC_{50})	vigabatrin [214]
Comment	vigabatrin is an irreversible inhibitor of GABA-T [214]

Nomenclature	aldehyde dehydrogenase 5 family, member A1 (succinic semialdehyde dehydrogenase)
Common abbreviation	SSADH
HGNC, UniProt	*ALDH5A1*, P51649
EC number	1.2.1.24: 4-oxobutanoate + NAD + H_2O = succinic acid + NADH + 2 H^+, 4-hydroxy-trans-2-nonenal + NAD + H_2O = 4-hydroxy-trans-2-nonenoate + NADH + 2 H^+
Cofactors	NAD

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Glycerophospholipid turnover

Overview: Phospholipids are the basic barrier components of membranes in eukaryotic cells divided into glycerophospholipids (phosphatidic acid, phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, phosphatidylinositol and its phosphorylated derivatives) and sphingolipids (ceramide phosphorylcholine and ceramide phosphorylethanolamine).

Phosphoinositide-specific phospholipase C

Overview: Phosphoinositide-specific phospholipase C (PLC, EC 3.1.4.11) catalyses the hydrolysis of PIP_2 to IP_3 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 are activated primarily by G protein-coupled receptors through members of the $G_{q/11}$ family of G proteins. The receptor-mediated activation of PLC-γ involves their phosphorylation by receptor tyrosine kinases (RTK) 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 G protein-coupled 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 [218], although this mechanism of action has been questioned [235]. The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC [257], although its selectivity among the isoforms is untested and it has been reported to occupy the H1 histamine receptor [230].

Nomenclature	PLCβ1	PLCβ2	PLCβ3	PLCβ4
HGNC, UniProt	*PLCB1*, Q9NQ66	*PLCB2*, Q00722	*PLCB3*, Q01970	*PLCB4*, Q15147
Endogenous activators	Gαq, Gα11, Gβγ [228,248,258]	Gα16, Gβγ, Rac2 (*RAC2*, P15153) [221,231-232,237,248]	Gαq, Gβγ [222,237,248]	Gαq [233]

Nomenclature	PLCγ1	PLCγ2	PLCδ1	PLCδ3	PLCδ4
HGNC, UniProt	*PLCG1*, P19174	*PLCG2*, P16885	*PLCD1*, P51178	*PLCD3*, Q8N3E9	*PLCD4*, Q9BRC7
Endogenous activators	PIP_3 [217]	PIP_3, Rac1 (*RAC1*, P63000), Rac2 (*RAC2*, P15153), Rac3 (*RAC3*, P60763) [217,251,263]	Transglutaminase II, p122-RhoGAP, spermine, Gβγ [225,229,244,248]	–	–
Endogenous inhibitors	–	–	Sphingomyelin [249]	–	–

Nomenclature	PLCε1	PLCζ1	PLCη1	PLCη2
HGNC, UniProt	*PLCE1*, Q9P212	*PLCZ1*, Q86YW0	*PLCH1*, Q4KWH8	*PLCH2*, O75038
Endogenous activators	Ras, rho [259,264]	–	–	Gβγ [266]

Comments: A series of PLC-like proteins (*PLCL1*, Q15111; *PLCL2*, Q9UPR0 and *PLCH1*, Q4KWH8) form a family with PLCδ and PLCζ1 isoforms, but appear to lack catalytic activity.

PLC-δ2 has been cloned from bovine sources [242].

Phospholipase A_2

Overview: Phospholipase A_2 (PLA_2, EC 3.1.1.4) 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	$sPLA_2$-1B	$sPLA_2$-2A	$sPLA_2$-2D	$sPLA_2$-2E	$sPLA_2$-2F	$sPLA_2$-3	$sPLA_2$-10	$sPLA_2$-12A
HGNC, UniProt	*PLA2G1B*, P04054	*PLA2G2A*, P14555	*PLA2G2D*, Q9UNK4	*PLA2G2E*, Q9NZK7	*PLA2G2F*, Q9BZM2	*PLA2G3*, Q9NZ20	*PLA2G10*, O15496	*PLA2G12A*, Q9BZM1

Cytosolic, calcium-dependent forms

Nomenclature	$cPLA_2$-4A	$cPLA_2$-4B	$cPLA_2$-4C	$cPLA_2$-4D	$cPLA_2$-4E	$cPLA_2$-4F
HGNC, UniProt	*PLA2G4A*, P47712	*PLA2G4B*, P0C869	*PLA2G4C*, Q9UP65	*PLA2G4D*, Q86XP0	*PLA2G4E*, Q3MJ16	*PLA2G4F*, Q68DD2
Comment	$cPLA_2$-4A also expresses lysophospholipase (EC 3.1.1.5) activity [256].	–	–	–	–	–

Other forms

Nomenclature	PLA_2-G5	$iPLA_2$-G6	PLA_2-G7	platelet-activating factor acetylhydrolase 2, 40kDa
HGNC, UniProt	*PLA2G5*, P39877	*PLA2G6*, O60733	*PLA2G7*, Q13093	*PAFAH2*, Q99487
Comment	–	–	–	PAFAH2 also expresses PAF hydrolase activity (EC 3.1.1.47)

Comments: The sequence of PLA_2-2C suggests a lack of catalytic activity, while PLA_2-12B (GXIIB, GXIII $sPLA_2$-like) appears to be catalytically inactive [254]. A further fragment has been identified with sequence similarities to Group II PLA_2 members. Otoconin 90 (OC90) shows sequence homology to PLA_2-G10.

A binding protein for secretory phospholipase A_2 has been identified which shows modest selectivity for $sPLA_2$-1B over $sPLA_2$-2A, and also binds snake toxin phospholipase A_2 [216]. The binding protein appears to have clearance function for circulating secretory phospholipase A_2, as well as signalling functions, and is a candidate antigen for idiopathic membraneous nephropathy [219].

PLA_2-G7 and PAFAH2 also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47).

Phosphatidylcholine-specific phospholipase D

Overview: Phosphatidylcholine-specific phospholipase D (PLD, EC 3.1.3.4) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction [253].

Nomenclature	PLD1	PLD2
HGNC, UniProt	*PLD1*, Q13393	*PLD2*, O14939
Endogenous activators	Arf1 (*ARF1*, P84077), PIP_2, RhoA, PKC evoked phosphorylation, RalA [226,241]	Arf1 (*ARF1*, P84077), oleic acid [255], PIP_2 [240]
Endogenous inhibitor	Gβγ [252]	Gβγ [252]
Selective inhibitors (pIC_{50})	–	VU0364739 (7.7) [236]

Comments: A lysophospholipase D activity (*ENPP2*, Q13822, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2, phosphodiesterase I, nucleotide pyrophosphatase 2, autotaxin) has been described, which not only catalyses the production of lysophosphatidic acid (LPA) from lysophosphatidylcholine, but also cleaves ATP (see Goding *et al.*, 2003 [224]). Additionally, an N-acylethanolamine-specific phospholipase D (*NAPEPLD*, Q6IQ20) has been characterized, which appears to have a role in the generation of endocannabinoids/endovanilloids, including anandamide [246]. This enzyme activity appears to be enhanced by polyamines in the physiological range [238] and fails to transphosphatidylate with alcohols [250].

Three further, less well-characterised isoforms are PLD3 (*PLD3*, Q8IV08, other names Choline phosphatase 3, HindIII K4L homolog, Hu-K4), PLD4 (*PLD4*, Q96BZ4, other names Choline phosphatase 4, Phosphatidylcholine-hydrolyzing phospholipase, D4C14orf175 UNQ2488/PRO5775) and PLD5 (*PLD5*, Q8N7P1). PLD3 has been reported to be involved in myogenesis [247]. PLD4 is described not to have phospholipase D catalytic activity [265], but has been associated with inflammatory disorders [245,260,262]. Sequence analysis suggests that PLD5 is catalytically inactive.

Lipid phosphate phosphatases

Overview: Lipid phosphate phosphatases, divided into phosphatidic acid phosphatases or lipins catalyse the dephosphorylation of phosphatidic acid (and other phosphorylated lipid derivatives) to generate inorganic PO_3^{4-} and diacylglycerol. PTEN, a phosphatase and tensin homolog (BZS, MHAM, MMAC1, PTEN1, TEP1) is a phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase which acts as a tumour suppressor by reducing cellular levels of PI 3,4,5-P, thereby toning down activity of PDK1 and PKB. Loss-of-function mutations are frequently identified as somatic mutations in cancers.

Nomenclature	Lipin1	Lipin2	Lipin3	PPA2A	PPA2B	PPA3A	phosphatase and tensin homolog
HGNC, UniProt	*LPIN1*, Q14693	*LPIN2*, Q92539	*LPIN3*, Q9BQK8	*PPAP2A*, O14494	*PPAP2B*, O14495	*PPAP2C*, O43688	*PTEN*, P60484
EC number	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.16, 3.1.3.48, 3.1.3.67
Substrates	–	phosphatidic acid	–	–	phosphatidic acid	–	phosphatidylinositol (3,4,5)-trisphosphate

Phosphatidylinositol kinases

Overview: Phosphatidylinositol may be phosphorylated at either 3- or 4- positions on the inositol ring by PI 3-kinases or PI 4-kinases, respectively.

Phosphatidylinositol 3-kinases Phosphatidylinositol 3-kinases (PI3K, provisional nomenclature) catalyse the introduction of a phosphate into the 3-position of phosphatidylinositol (PI), phosphatidylinositol 4-phosphate (PIP) or phosphatidylinositol 4,5-bisphosphate (PIP2). There is evidence that PI3K can also phosphorylate serine/threonine residues on proteins. In addition to the classes described below, further serine/threonine protein kinases, including ATM (Q13315) and mTOR (P42345), have been described to phosphorylate phosphatidylinositol and have been termed PI3K-related kinases. Structurally, PI3K have common motifs of at least one C2, calcium-binding domain and helical domains, alongside structurally-conserved catalytic domains. wortmannin and LY294002 are widely-used inhibitors of PI3K activities. wortmannin is irreversible and shows modest selectivity between Class I and Class II PI3K, while LY294002 is reversible and selective for Class I compared to Class II PI3K.

Class I PI3Ks (EC 2.7.1.153) phosphorylate phosphatidylinositol 4,5-bisphosphate to generate phosphatidylinositol 3,4,5-trisphosphate and are heterodimeric, matching catalytic and regulatory subunits. Class IA PI3Ks include p110α, p110β and p110δ catalytic subunits, with predominantly p85 and p55 regulatory subunits. The single catalytic subunit that forms Class IB PI3K is p110γ. Class IA PI3Ks are more associated with receptor tyrosine kinase pathways, while the Class IB PI3K is linked more with GPCR signalling.

Subunits

Nomenclature	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit beta	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit gamma
Common abbreviation	p110α/PIK3CA	p110β/PIK3CB	p110δ/PIK3CD	p110γ/PIK3CG
HGNC, UniProt	*PIK3CA*, P42336	*PIK3CB*, P42338	*PIK3CD*, O00329	*PIK3CG*, P48736
EC number	2.7.1.153, 2.7.11.1	2.7.1.153	2.7.1.153	2.7.1.153
Selective inhibitors (pIC_{50})	–	–	–	CZC 24832 (pK_d 7.7) [220]

Nomenclature	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	phosphoinositide-3-kinase, regulatory subunit 2 (beta)	phosphoinositide-3-kinase, regulatory subunit 3 (gamma)	phosphoinositide-3-kinase, regulatory subunit 4	phosphoinositide-3-kinase, regulatory subunit 5	phosphoinositide-3-kinase, regulatory subunit 6
Common abbreviation	p85α/PIK3R1	p85β/PIK3R2	p55γ/PIK3R3	p150/VPS15/PIK3R4	p101/PIK3R5	p87/PIK3R6
HGNC, UniProt	*PIK3R1*, P27986	*PIK3R2*, O00459	*PIK3R3*, Q92569	*PIK3R4*, Q99570	*PIK3R5*, Q8WYR1	*PIK3R6*, Q5UE93
EC number	–	–	–	2.7.11.1	–	–

Class II PI3Ks (EC 2.7.1.154) phosphorylate phosphatidylinositol to generate phosphatidylinositol 3-phosphate (and possibly phosphatidylinositol 4-phosphate to generate phosphatidylinositol 3,4-bisphosphate). Three monomeric members exist, PI3K-C2α, β and γ, and include Ras-binding, Phox homology and two C2domains.

Nomenclature	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 alpha	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 beta	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 gamma
Common abbreviation	C2α/PIK3C2A	C2β/PIK3C2B	C2γ/PIK3C2G
HGNC, UniProt	*PIK3C2A*, O00443	*PIK3C2B*, O00750	*PIK3C2G*, O75747
EC number	2.7.1.154	2.7.1.154	2.7.1.154

The only **class III PI3K** isoform (EC 2.7.1.137) is a heterodimer formed of a catalytic subunit (VPS34) and regulatory subunit (VPS15).

Nomenclature	phosphatidylinositol 3-kinase, catalytic subunit type 3	phosphoinositide-3-kinase, regulatory subunit 4
Common abbreviation	VPS34/PIK3C3	p150/VPS15/PIK3R4
HGNC, UniProt	*PIK3C3*, Q8NEB9	*PIK3R4*, Q99570

Phosphatidylinositol 4-kinases Phosphatidylinositol 4-kinases (EC 2.7.1.67) generate phosphatidylinositol 4-phosphate and may be divided into higher molecular weight type III and lower molecular weight type II forms.

Nomenclature	phosphatidylinositol 4-kinase, catalytic, alpha	phosphatidylinositol 4-kinase, catalytic, beta	phosphatidylinositol 4-kinase type 2 alpha	phosphatidylinositol 4-kinase type 2 beta
Common abbreviation	PI4KIIIα/PIK4CA	PI4KIIIβ/PIK4CB	PI4KIIα/PI4K2A	PI4KIIβ/PI4K2B
HGNC, UniProt	*PI4KA*, P42356	*PI4KB*, Q9UBF8	*PI4K2A*, Q9BTU6	*PI4K2B*, Q8TCG2
Endogenous activation	–	PKD-mediated phosphorylation [227]	–	–
(Sub)family-selective inhibitors (pIC_{50})	wortmannin (6.7 – 6.8) [223,243]	wortmannin (6.7 – 6.8) [223,243]	adenosine (4.5 – 5.0) [261]	adenosine (4.5 – 5.0) [261]
Selective inhibitors (pIC_{50})	–	PIK-93 [234]	–	–

Comments: wortmannin also inhibits type III phosphatidylinositol 4-kinases and polo-like kinase [239]. PIK93 also inhibits PI 3-kinases [234]. Adenosine activates adenosine receptors.

Phosphatidylinositol phosphate kinases

Overview: PIP_2 is generated by phosphorylation of PI 4-phosphate or PI 5-phosphate by type I PI 4-phosphate 5-kinases or type II PI 5-phosphate 4-kinases.

Nomenclature	phosphatidylinositol-4-phosphate 5-kinase, type I, alpha	phosphatidylinositol-4-phosphate 5-kinase, type I, beta	phosphatidylinositol-4-phosphate 5-kinase, type I, gamma
Common abbreviation	PIP5K1A	PIP5K1B	PIP5K1C
HGNC, UniProt	*PIP5K1A*, Q99755	*PIP5K1B*, O14986	*PIP5K1C*, O60331
EC number	2.7.1.68	2.7.1.68	2.7.1.68

Nomenclature	phosphatidylinositol-5-phosphate 4-kinase, type II, alpha	phosphatidylinositol-5-phosphate 4-kinase, type II, beta	phosphatidylinositol-5-phosphate 4-kinase, type II, gamma
Common abbreviation	PIP4K2A	PIP4K2B	PIP4K2G
HGNC, UniProt	*PIP4K2A*, P48426	*PIP4K2B*, P78356	*PIP4K2C*, Q8TBX8
EC number	2.7.1.149	2.7.1.149	2.7.1.149

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Haem oxygenase

Overview: Haem oxygenase (heme,hydrogen-donor:oxygen oxidoreductase (α-methene-oxidizing, hydroxylating)), E.C. 1.14.99.3, converts heme into biliverdin and carbon monoxide, utilizing NADPH as cofactor.

Nomenclature	Haem oxygenase 1	Haem oxygenase 2
Common abbreviation	HO1	HO2
HGNC, UniProt	*HMOX1*, P09601	*HMOX2*, P30519
EC number	1.14.99.3	1.14.99.3

Comments: The existence of a third non-catalytic version of haem oxygenase, HO3, has been proposed, although this has been suggested to be a pseudogene [268]. The chemical tin protoporphyrin IX acts as a haem oxygenase inhibitor in rat liver with an IC_{50} value of 11 nM [267].

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Hydrogen sulfide synthesis

Overview: Hydrogen sulfide is a putative gasotransmitter, with similarities to NO and carbon monoxide. Although the enzymes indicated have multiple enzymatic activities, the focus here is the generation of hydrogen sulfide and the enzymatic characteristics are described accordingly. Cystathionine β-synthase and cystathionine γ-lyase are pyridoxal phosphate-dependent enzymes, while L-cysteine:2-oxoglutarate aminotransferase and 3-mercaptopyruvate sulfurtransferase function in combination as a pyridoxal phosphate-independent pathway.

Nomenclature	Cystathionine β-synthase	Cystathionine γ-lyase	L-Cysteine:2-oxoglutarate aminotransferase	3-Mercaptopyruvate sulfurtransferase
Common abbreviation	CBS	CSE	CAT	MPST
HGNC, UniProt	*CBS*, P35520	*CTH*, P32929	*CCBL1*, Q16773	*MPST*, P25325
EC number	4.2.1.22	4.4.1.1	4.4.1.13	2.8.1.2
Endogenous substrates	L-homocysteine, L-cysteine (Km 6x10^{-3} M) [269]	L-cysteine	L-cysteine	3-mercaptopyruvic acid (Km 1.2x10^{-3} M) [270]
Products	cystathionine	NH_3, pyruvic acid	NH_3, pyruvic acid	pyruvic acid
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	Zn^{2+}
Inhibitors (pIC_{50})	aminooxyacetic acid	propargylglycine	–	–

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Inositol phosphate turnover

Overview: The sugar alcohol D-*myo*-inositol is a component of the phosphatidylinositol signalling cycle, where the principal second messenger is inositol 1,4,5-trisphosphate, IP_3, which acts at intracellular ligand-gated ion channels, IP_3 receptors to elevate intracellular calcium. IP_3 is recycled to inositol by phosphatases or phosphorylated to form other active inositol polyphosphates. Inositol produced from dephosphorylation of IP_3 is recycled into membrane phospholipid under the influence of phosphatidyinositol synthase activity (CDP-diacylglycerol-inositol 3-phosphatidyltransferase [EC 2.7.8.11]).

Inositol 1,4,5-trisphosphate 3-kinases

Overview: Inositol 1,4,5-trisphosphate 3-kinases (E.C. 2.7.1.127, ENSFM00250000001260) catalyse the generation of inositol 1,3,4,5-tetrakisphosphate (IP_4) from IP_3. IP_3 kinase activity is enhanced in the presence of calcium/calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158) [271].

Nomenclature	IP_3 kinase A	IP_3 kinase B	IP_3 kinase C
HGNC, UniProt	*ITPKA*, P23677	*ITPKB*, P27987	*ITPKC*, Q96DU7

Inositol polyphosphate phosphatases

Overview: Members of this family exhibit phosphatase activity towards IP_3, as well as towards other inositol derivatives, including the phospholipids PIP_2 and PIP_3. With IP_3 as substrate, 1-phosphatase (EC 3.1.3.57) generates 4,5,-IP_2, 4-phosphatases (EC 3.1.3.66, ENSFM00250000001432) generate 1,5,-IP_2 and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4,-IP_2.

Nomenclature	INPP1	INPP4A, INPP4B	INPP5A, INPP5B, INPP5D, INPP5E, INPP5J, INPP5K, INPPL1, OCRL, SYNJ1, SYNJ2
HGNC, UniProt	*INPP1*, P49441	*INPP4A*, Q96PE3; *INPP4B*, O15327	*INPP5A*, Q14642; *INPP5B*, P32019; *INPP5D*, Q92835; *INPP5E*, Q9NRR6; *INPP5J*, Q15735; *INPP5K*, Q9BT40; *INPPL1*, O15357; *OCRL*, Q01968; *SYNJ1*, O43426; *SYNJ2*, O15056
EC number	3.1.3.57	3.1.3.36, 3.1.3.36	3.1.3.56, 3.1.3.56, 3.1.3.86, 3.1.3.36, 3.1.3.56, 3.1.3.56, 3.1.3.86, 3.1.3.36, 3.1.3.36, 3.1.3.36

Comments: *In vitro* analysis suggested IP_3 and IP_4 were poor substrates for SKIP, synaptojanin 1 and synaptojanin 2, but suggested that PIP_2 and PIP_3 were more efficiently hydrolysed [276].

Inositol monophosphatase

Overview: Inositol monophosphatase (E.C. 3.1.3.25, IMPase, *myo*-inositol-1(or 4)-phosphate phosphohydrolase) is a magnesium-dependent homodimer which hydrolyses *myo*-inositol monophosphate to generate *myo*-inositol and PO_3^{4-}. glycerol may be a physiological phosphate acceptor. lithium is a nonselective un-competitive inhibitor more potent at IMPase 1 (pK_i *ca.* 3.5, [274]; pIC_{50} 3.2, [275]) than IMPase 2 (pIC_{50} 1.8–2.1, [275]). IMPase activity may be inhibited competitively by L690330 (pK_i 5.5, [274]), although the enzyme selectivity is not yet established.

Nomenclature	IMPase 1	IMPase 2
HGNC, UniProt	*IMPA1*, P29218	*IMPA2*, O14732
EC number	3.1.3.25	3.1.3.25
Rank order of affinity	inositol 4-phosphate > inositol 3-phosphate > inositol 1-phosphate [274]	–

Comments: Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder [277–279]. Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of lithium in mice [272–273].

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Lanosterol biosynthesis pathway

Overview: Lanosterol is a precursor for cholesterol, which is synthesized primarily in the liver in a pathway often described as the mevalonate or HMG-CoA reductase pathway. The first two steps (formation of acetoacetyl CoA and the mitochondrial generation of HMG-CoA) are also associated with oxidation of fatty acids.

Nomenclature	acetyl-CoA acetyltransferase 1	acetyl-CoA acetyltransferase 2
HGNC, UniProt	*ACAT1*, P24752	*ACAT2*, Q9BWD1
EC number	2.3.1.9: acetyl CoA + acetyl CoA = acetoacetyl CoA + coenzyme A	2.3.1.9: acetyl CoA + acetyl CoA = acetoacetyl CoA + coenzyme A

Nomenclature	hydroxymethylglutaryl-CoA synthase 1	hydroxymethylglutaryl-CoA synthase 2
HGNC, UniProt	*HMGCS1*, Q01581	*HMGCS2*, P54868
EC number	2.3.3.10: acetyl CoA + H_2O + acetoacetyl CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A	2.3.3.10: acetyl CoA + H_2O + acetoacetyl CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A
Comment	HMGCoA synthase is found in cytosolic and mitochondrial versions; the former associated with (R)-mevalonate synthesis and the latter with ketogenesis.	–

Nomenclature	hydroxymethylglutaryl-CoA reductase
HGNC, UniProt	*HMGCR*, P04035
EC number	1.1.1.34: (S)-3-hydroxy-3-methylglutaryl-CoA + NADPH -> (R)-mevalonate + coenzyme A + NADP+
Selective inhibitors (pIC_{50})	lovastatin (Competitive) (pK_i 9.22) [280], rosuvastatin (Competitive) (8.3) [283], atorvastatin (Competitive) (8.1) [283], simvastatin (Competitive) (7.96) [283], fluvastatin (Competitive) (7.55) [283]
Comment	HMGCoA reductase is associated with intracellular membranes; enzymatic activity is inhibited by phosphorylation by AMP-activated kinase. The enzymatic reaction is a three-step reaction involving the intermediate generation of mevaldehyde-CoA and mevaldehyde.

Nomenclature	mevalonate kinase
HGNC, UniProt	*MVK*, Q03426
EC number	2.7.1.36: ATP + (R)-mevalonate -> ADP + (R)-5-phosphomevalonate
Comment	Mevalonate kinase activity is regulated by the downstream products farnesyl diphosphate and geranyl diphosphate as an example of feedback inhibition.

Nomenclature	phosphomevalonate kinase
HGNC, UniProt	*PMVK*, Q15126
EC number	2.7.4.2: ATP + (R)-5-phosphomevalonate = ADP + (R)-5-diphosphomevalonate

Nomenclature	diphosphomevalonate decarboxylase
HGNC, UniProt	*MVD*, P53602
EC number	4.1.1.33: ATP + (R)-5-diphosphomevalonate -> ADP + isopentenyl diphosphate + PO_3^{4-} + CO_2

Nomenclature	isopentenyl-diphosphate Δ-isomerase 1	isopentenyl-diphosphate Δ-isomerase 2
HGNC, UniProt	*IDI1*, Q13907	*IDI2*, Q9BXS1
EC number	5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate	5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate

Nomenclature	geranylgeranyl diphosphate synthase
HGNC, UniProt	*GGPS1*, O95749
EC number	2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate ion, 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate ion, 2.5.1.29: trans,trans-farnesyl diphosphate + isopentenyl diphosphate -> geranylgeranyl diphosphate + diphosphate ion

Nomenclature	farnesyl diphosphate synthase
HGNC, UniProt	*FDPS*, P14324
EC number	2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate ion, 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate ion
Selective inhibitors (pIC_{50})	risedronate (8.4) [281], alendronate (6.34) [281]

Nomenclature	squalene synthase
HGNC, UniProt	*FDFT1*, P37268
EC number	2.5.1.21: 2 trans,trans-farnesyl diphosphate -> presqualene diphosphate + diphosphate ion, presqualene diphosphate + NAD(P)H + H^+ -> squalene + diphosphate + $NAD(P)^+$
Cofactors	NADPH [285]
Selective inhibitors (pIC_{50})	zaragozic acid A (pK_i 10.1 - Rat) [282], FTI 276 (9.3) [284], zaragozic acid A (9.15) [286]

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Peptidases and proteinases

Overview: Peptidases and proteinases hydrolyse peptide bonds, and can be simply divided on the basis of whether terminal peptide bonds are cleaved (exopeptidases and exoproteinases) at the amino terminus (aminopeptidases) or carboxy terminus (carboxypeptidases). Non-terminal peptide bonds are cleaved by endopeptidases and endoproteinases, which are divided into serine endopeptidases (EC 3.4.21.-), cysteine endopeptidases (EC 3.4.22.-), aspartate endopeptidases (EC 3.4.23.-), metalloendopeptidases (EC 3.4.24.-) and threonine endopeptidases (EC 3.4.25.-). It is beyond the scope of the Guide to list all peptidase and proteinase activities; this summary focuses on selected enzymes of significant pharmacological interest.

Cysteine (C) Peptidases: Caspases

Overview: Caspases, (E.C. 3.4.22.-) which derive their name from Cysteine ASPartate-specific proteASES, include at least two families; initiator caspases (caspases 2, 8, 9 and 10), which are able to hydrolyse and activate a second family of effector caspases (caspases 3, 6 and 7), which themselves are able to hydrolyse further cellular proteins to bring about programmed cell death. Caspases are heterotetrameric, being made up of two pairs of subunits, generated by a single gene product, which is proteolysed to form the mature protein. Members of the mammalian inhibitors of apoptosis proteins (IAP) are able to bind the procaspases, thereby preventing maturation to active proteinases.

Nomenclature	Caspase 1	Caspase 2	Caspase 3	Caspase 4
HGNC, UniProt	*CASP1*, P29466	*CASP2*, P42575	*CASP3*, P42574	*CASP4*, P49662
EC number	3.4.22.36	3.4.22.55	3.4.22.56	3.4.22.57
Endogenous activators	–	–	Caspase 8, caspase 9, caspase 10, GrB	–
Endogenous substrates	Rho GDP dissociation inhibitor beta, parkin, pro-caspase 4, pro-interleukin-1β	–	huntingtin, retinoblastoma-associated protein, caspase 3, ICAD, PARP, PKCδ, pro-caspase 7	pro-caspase 1
Activators	–	–	PAC1 [301], PETCM [295]	–
Selective inhibitors (pIC_{50})	Z-YVAD-FMK [287]	Z-VDVAD-FMK [291]	AZ10417808 [303], Z-DEVD-FMK [288], Z-DQMD-FMK [294]	–
Comment	Consists of caspase-1 subunit p20 and caspase-1 subunit p10 (see Uniprot entry)	Consists of caspase-2 subunit p18, caspase-2 subunit p13, and caspase-2 subunit p12 (see Uniprot entry)	Consists of caspase-3 subunit p17 and caspase-3 subunit p12 (see Uniprot entry)	Consists of caspase-4 subunit 1 and caspase-4 subunit 2 (see Uniprot entry)

Nomenclature	Caspase 5	Caspase 6	Caspase 7	Caspase 8
HGNC, UniProt	*CASP5*, P51878	*CASP6*, P55212	*CASP7*, P55210	*CASP8*, Q14790
EC number	3.4.22.58	3.4.22.59	3.4.22.60	3.4.22.61
Endogenous activators	–	Caspase 8, caspase 9, caspase 10, GrB	Caspase 8, caspase 9, caspase 10, GrB	DISC
Endogenous substrates	–	–	huntingtin, retinoblastoma-associated protein, caspase 3, ICAD, PARP, PKCδ, Pro-caspase 7	BH3 interacting-domain death agonist, FLICE-like inhibitory protein, caspase 8, pro-caspase 3, pro-caspase 6, pro-caspase 7
Selective inhibitors (pIC_{50})	Z-WEHD-FMK [299]	Z-VEID-FMK [302]	–	Z-IETD-FMK [293]
Comment	Consists of **caspase-5 subunit p20** and **caspase-5 subunit p10** (see Uniprot entry)	Consists of **caspase-6 subunit p18** and **caspase-6 subunit p11** (see Uniprot entry)	Consists of **caspase-7 subunit p20** and **caspase-7 subunit p11** (see Uniprot entry)	Consists of **caspase-8 subunit p18** and **caspase-8 subunit p10** (see Uniprot entry)

Nomenclature	Caspase 9	Caspase 10	Caspase 14
HGNC, UniProt	*CASP9*, P55211	*CASP10*, Q92851	*CASP14*, P31944
EC number	3.4.22.62	3.4.22.63	3.4.22.-
Endogenous activators	–	DISC	–
Endogenous substrates	caspase 9, PARP, pro-caspase 3, pro-caspase 6, pro-caspase 7	caspase 10, pro-caspase 3, pro-caspase 6, pro-caspase 7	–
Selective inhibitors (pIC_{50})	Z-LEHD-FMK [298]	–	–
Comment	Consists of **caspase-9 subunit p35** and **caspase-9 subunit p10** (see Uniprot entry)	Consists of **caspase-10 subunit p23/17** and **caspase-10 subunit p12** (see Uniprot entry)	Consists of **caspase-14 subunit p19** and **caspase-14 subunit p10** (see Uniprot entry)

Comments: CARD16 (Caspase recruitment domain-containing protein 16, caspase-1 inhibitor COP, CARD only domain-containing protein 1, pseudo interleukin-1β converting enzyme, pseudo-ICE, ENSG00000204397) shares sequence similarity with some of the caspases.

Metallo (M) Peptidases

Nomenclature	Aminopeptidase A	Leucyl-cysteinyl aminopeptidase	Leukotriene A_4 hydrolase	Neutral endopeptidase
HGNC, UniProt	*DNPEP*, Q9ULA0	*LNPEP*, Q9UIQ6	*LTA4H*, P09960	*MME*, P08473
EC number	3.4.11.21	3.4.11.3	3.3.2.6	3.4.24.11
Endogenous substrates	–	–	LTA_4	enkephalins
Selective inhibitors (pIC_{50})	–	–	–	thiorphan
Inhibitors (pIC_{50})	–	–	bestatin [300]	–
Comment	Hydrolyses CCK-8 (*CCK*, P06307) [297], angiotensin II (*AGT*, P01019) [307], neurokinin B (*TAC3*, Q9UHF0), chromogranin A (*CHGA*, P10645), kallidin (*KNG1*, P01042) [292]	Hydrolyses AVP (*AVP*, P01178), oxytocin (*OXT*, P01178), kallidin (*KNG1*, P01042), [Met]enkephalin (*PENK*, P01210), dynorphin A (*PDYN*, P01213)	–	–

Nomenclature	Angiotensin-converting enzyme	Angiotensin-converting enzyme 2	Endothelin-converting enzyme 1	Endothelin-converting enzyme 2
Common abbreviation	ACE1	ACE2	ECE1	ECE2
HGNC, UniProt	*ACE*, P12821	*ACE2*, Q9BYF1	*ECE1*, P42892	*ECE2*, O60344
EC number	3.4.15.1	3.4.15.1	3.4.24.71	3.4.24.71
Endogenous substrates	angiotensin I (*AGT*, P01019) > angiotensin II (*AGT*, P01019)	angiotensin I (*AGT*, P01019) > angiotensin-(1-9) (*AGT*, P01019) [290]	ET-1 (*EDN1*, P05305), ET-2 (*EDN2*, P20800), ET-3 (*EDN3*, P14138)	ET-1 (*EDN1*, P05305), ET-2 (*EDN2*, P20800), ET-3 (*EDN3*, P14138)
Selective inhibitors (pIC_{50})	captopril	captopril	SM19712 [305]	–
Comment	Hip-His Leu has been used experimentally as a probe for ACE1. ACE1 appears to express a distinct GPI hydrolase activity [296].	Abz-Ser-Pro-Tyr(NO_2)-OH has been used experimentally as a probe for ACE2	–	–

Nomenclature	Aminopeptidase N	Aminopeptidase O	Aminopeptidase Q	Arginyl aminopeptidase	Arginyl aminopeptidase-like 1	Aminopeptidase-like 1
HGNC, UniProt	*ANPEP*, P15144	*C9orf3*, Q8N6M6	–, Q6Q4G3	*RNPEP*, Q9H4A4	*RNPEPL1*, Q9HAU8	*NPEPL1*, Q8NDH3
EC number	3.4.11.2	3.4.11.-	3.4.11.-	3.4.11.6	3.4.11.-	3.4.11.-

Nomenclature	Endoplasmic reticulum aminopeptidase 1	Endoplasmic reticulum aminopeptidase 2	Glutamyl aminopeptidase	Leucine aminopeptidase 3	Methionyl aminopeptidase 1	Methionyl aminopeptidase 2
HGNC, UniProt	*ERAP1*, Q9NZ08	*ERAP2*, Q6P179	*ENPEP*, Q07075	*LAP3*, P28838	*METAP1*, P53582	*METAP2*, P50579
EC number	3.4.11.-	3.4.11.-	3.4.11.7	3.4.11.1	3.4.11.3, 3.4.11.18	3.4.11.18

Nomenclature	Methionyl aminopeptidase type 1D (mitochondrial)	Puromycin-sensitive aminopeptidase	Puromycin-sensitive aminopeptidase-like protein	TRH-specific aminopeptidase	X-prolyl aminopeptidase 1	X-prolyl aminopeptidase 2
HGNC, UniProt	*METAP1D*, Q6UB28	*NPEPPS*, P55786	–	*TRHDE*, Q9UKU6	*XPNPEP1*, Q9NQW7	*XPNPEP2*, O43895
EC number	3.4.11.18	3.4.11.14	–	3.4.19.6	3.4.11.9	3.4.11.9

Nomenclature	X-prolyl aminopeptidase 3	Carboxypeptidase D	AE binding protein 1	Carboxypeptidase A1 (pancreatic)	Carboxypeptidase A2 (pancreatic)	Carboxypeptidase A3 (mast cell)
HGNC, UniProt	*XPNPEP3*, Q9NQH7	*CPD*, O75976	*AEBP1*, Q8IUX7	*CPA1*, P15085	*CPA2*, P48052	*CPA3*, P15088
EC number	3.4.11.9	3.4.17.22	–	3.4.17.1	3.4.17.15	3.4.17.1

Nomenclature	Carboxypeptidase A4	Carboxypeptidase A5	Carboxypeptidase A6	Carboxypeptidase B1 (tissue)	Carboxypeptidase B2 (plasma)	Carboxypeptidase E
HGNC, UniProt	*CPA4*, Q9UI42	*CPA5*, Q8WXQ8	*CPA6*, Q8N4T0	*CPB1*, P15086	*CPB2*, Q96IY4	*CPE*, P16870
EC number	3.4.17.-	3.4.17.1	3.4.17.1	3.4.17.2	3.4.17.20	3.4.17.10

Nomenclature	Carboxypeptidase M	Carboxypeptidase N, polypeptide 1	Carboxypeptidase N, polypeptide 2	Carboxypeptidase O	Carboxypeptidase Q	Carboxypeptidase X (M14 family), member 1
HGNC, UniProt	*CPM*, P14384	*CPN1*, P15169	*CPN2*, P22792	*CPO*, Q8IVL8	*CPQ*, –	*CPXM1*, Q96SM3
EC number	3.4.17.12	3.4.17.3	–	3.4.17.-	–	3.4.17.-

Nomenclature	Carboxypeptidase X (M14 family), member 2	Carboxypeptidase Z	Carnosine dipeptidase 1 (metallopeptidase M20 family)	Carnosine dipeptidase 2	Folate hydrolase (prostate-specific membrane antigen) 1	Folate hydrolase 1B
HGNC, UniProt	*CPXM2*, Q8N436	*CPZ*, Q66K79	*CNDP1*, Q96KN2	*CNDP2*, Q96KP4	*FOLH1*, Q04609	*FOLH1B*, Q9HBA9
EC number	–	3.4.17.-	3.4.13.20	3.4.13.18	3.4.17.21	–

Nomenclature	N-Acetylated α-linked acidic dipeptidase-like 1	N-Acetylated α-linked acidic dipeptidase 2
HGNC, UniProt	*NAALADL1*, Q9UQQ1	*NAALAD2*, Q9Y3Q0
EC number	3.4.17.21	3.4.17.21

Matrix metallopeptidases

Overview: Matrix metalloproteinases (MMP) are calcium- and zinc-dependent proteinases regulating the extracellular matrix and are often divided (*e.g.* [306]) on functional and structural bases into gelatinases, collagenases, stromyelinases and matrilysins, as well as membrane type-MMP (MT-MMP).

Nomenclature	MMP1	MMP2	MMP3	MMP7	MMP8	MMP9
HGNC, UniProt	*MMP1*, P03956	*MMP2*, P08253	*MMP3*, P08254	*MMP7*, P09237	*MMP8*, P22894	*MMP9*, P14780
EC number	3.4.24.7	3.4.24.24	3.4.24.17	3.4.24.23	3.4.24.34	3.4.24.35
Selective inhibitors (pIC_{50})	–	ARP100 [304]	–	–	–	–

Nomenclature	MMP10	MMP11	MMP12	MMP13	MMP14	MMP15
HGNC, UniProt	*MMP10*, P09238	*MMP11*, P24347	*MMP12*, P39900	*MMP13*, P45452	*MMP14*, P50281	*MMP15*, P51511
EC number	3.4.24.22	3.4.24.-	3.4.24.65	3.4.24.-	3.4.24.80	3.4.24.-
Selective inhibitors (pIC50)	–	–	–	CL82198 [289], WAY170523 [289]	–	–

Nomenclature	MMP16	MMP17	MMP19	MMP20	MMP21	MMP23	MMP24
HGNC, UniProt	*MMP16*, P51512	*MMP17*, Q9ULZ9	*MMP19*, Q99542	*MMP20*, O60882	*MMP21*, Q8N119	*MMP23B*, O75900	*MMP24*, Q9Y5R2
EC number	3.4.24.-	3.4.24.-	3.4.24.-	3.4.24.-	3.4.24.-	3.4.24.-	3.4.24.-

Nomenclature	MMP25	MMP26	MMP27	MMP28
HGNC, UniProt	*MMP25*, Q9NPA2	*MMP26*, Q9NRE1	*MMP27*, Q9H306	*MMP28*, Q9H239
EC number	3.4.24.-	3.4.24.-	3.4.24.-	3.4.24.-

Comments: A number of small molecule 'broad spectrum' inhibitors of MMP have been described, including marimastat and batimastat.

Tissue inhibitors of metalloproteinase (TIMP) proteins are endogenous inhibitors acting to chelate MMP proteins: TIMP1 (*TIMP1*, P01033), TIMP2 (*TIMP2*, P16035), TIMP3 (*TIMP3*, P35625), TIMP4 (*TIMP4*, Q99727)

ADAM metallopeptidases

Overview: ADAM (A Disintegrin And Metalloproteinase domain containing proteins) metalloproteinases cleave cell-surface or transmembrane proteins to generate soluble and membrane-limited products.

Nomenclature	ADAM2	ADAM7	ADAM8	ADAM9	ADAM10	ADAM11	ADAM12	ADAM15	ADAM17
HGNC, UniProt	*ADAM2*, Q99965	*ADAM7*, Q9H2U9	*ADAM8*, P78325	*ADAM9*, Q13443	*ADAM10*, O14672	*ADAM11*, O75078	*ADAM12*, O43184	*ADAM15*, Q13444	*ADAM17*, P78536
EC number	–	–	3.4.24.-	3.4.24.-	3.4.24.81	–	3.4.24.-	–	3.4.24.86

Nomenclature	ADAM18	ADAM19	ADAM20	ADAM21	ADAM22	ADAM23	ADAM28	ADAM29	ADAM30	ADAM32	ADAM33
HGNC, UniProt	*ADAM18*, Q9Y3Q7	*ADAM19*, Q9H013	*ADAM20*, O43506	*ADAM21*, Q9UKJ8	*ADAM22*, Q9P0K1	*ADAM23*, O75077	*ADAM28*, Q9UKQ2	*ADAM29*, Q9UKF5	*ADAM30*, Q9UKF2	*ADAM32*, Q8TC27	*ADAM33*, Q9BZ11
EC number	–	–	–	–	–	–	–	–	–	–	3.4.24.-

Comments: Additional family members include AC123767.2 (cDNA FLJ58962, moderately similar to mouse ADAM3, ENSG00000231168), AL160191.3 (ADAM21-like protein, ENSG00000235812), AC136428.3-2 (ENSG00000185520) and ADAMDEC1 (decysin 1, ENSG00000134028).

ADAMTS metallopeptidases

Overview: ADAMTS (with thrombospondin motifs) metalloproteinases cleave cell-surface or transmembrane proteins to generate soluble and membrane-limited products.

Nomenclature	ADAMTS1	ADAMTS2	ADAMTS3	ADAMTS4	ADAMTS5	ADAMTS6	ADAMTS7	ADAMTS8	ADAMTS9	ADAMTS10
HGNC, UniProt	*ADAMTS1*, Q9UHI8	*ADAMTS2*, O95450	*ADAMTS3*, O15072	*ADAMTS4*, O75173	*ADAMTS5*, Q9UNA0	*ADAMTS6*, Q9UKP5	*ADAMTS7*, Q9UKP4	*ADAMTS8*, Q9UP79	*ADAMTS9*, Q9P2N4	*ADAMTS10*, Q9H324
EC number	3.4.24.-	3.4.24.14	–	3.4.24.82	3.4.24.-	–	–	–	–	–

Nomenclature	ADAMTS12	ADAMTS13	ADAMTS14	ADAMTS15	ADAMTS16	ADAMTS17	ADAMTS18	ADAMTS19	ADAMTS20
HGNC, UniProt	*ADAMTS12*, P58397	*ADAMTS13*, Q76LX8	*ADAMTS14*, Q8WXS8	*ADAMTS15*, Q8TE58	*ADAMTS16*, Q8TE57	*ADAMTS17*, Q8TE56	*ADAMTS18*, Q8TE60	*ADAMTS19*, Q8TE59	*ADAMTS20*, P59510
Comment	–	Loss-of-function mutations of autoimmune antibodies are associated with thrombotic thrombocytopenic purpura	–	–	–	–	–	–	–

Comments: Other family members include AC104758.12-5 (FLJ00317 protein Fragment ENSG00000231463), AC139425.3-1 (ENSG00000225577), and AC126339.6-1 (ENSG00000225734).

Serine (S) Peptidases

Nomenclature	Cathepsin A	Vitellogenic carboxypeptidase-like protein	Prolylcarboxypeptidase	Serine carboxypeptidase 1	Dipeptidyl peptidase 4	Dipeptidyl-peptidase 7
HGNC, UniProt	*CTSA*, P10619	*CPVL*, Q9H3G5	*PRCP*, P42785	*SCPEP1*, Q9HB40	*DPP4*, P27487	*DPP7*, Q9UHL4
EC number	3.4.16.5	3.4.16.-	3.4.16.2	3.4.16.-	3.4.14.5	3.4.14.2
Endogenous substrates	–	–	–	–	glucagon-like peptide 1	–

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Protein serine/threonine kinases

N.B. Further enzymes can be found on the GuidetoPHARMACOLOGY.org website.

Overview: Protein serine/threonine kinases (E.C. 2.7.11.-) use the co-substrate ATP to phosphorylate serine and/or threonine residues on target proteins. Analysis of the human genome suggests the presence of 518 protein kinases in man, with over 100 protein kinase-like pseudogenes [342]. It is beyond the scope of the Guide to list all these protein kinase activities; this summary focuses on AGC protein kinases associated with GPCR signalling, which may be divided into 15 subfamilies in man.

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 [319].

G protein-coupled receptor kinases

Overview: G protein-coupled receptor kinases, epitomized by βARK, are involved in the rapid phosphorylation and desensitization of GPCR. Classically, high concentrations of β_2-adrenoceptor agonists binding to the receptor lead to the consequent activation and dissociation of the heterotrimeric G protein G_s. $G\alpha_s$ activates adenylyl cyclase activity, while $G\beta\gamma$ subunits perform other functions, one of which is to recruit βARK to phosphorylate serine/threonine residues in the cytoplasmic tail of the β_2-adrenoceptor. The phosphorylated receptor binds, with high affinity, a member of the arrestin family (ENSFM00250000000572), which prevents further signalling through the G protein (uncoupling) and may allow interaction with scaffolding proteins, such as clathrin, with the possible consequence of internalization and/or degradation.

Nomenclature	Common abbreviation	HGNC, UniProt	EC number	Comment
G protein-coupled receptor kinase 1	GRK1	*GRK1*, Q15835	2.7.11.14	–
beta adrenergic receptor kinase 1	GRK2	*ADRBK1*, P25098	2.7.11.15	Protein kinase C-mediated phosphorylation increases membrane association [316,353]
beta adrenergic receptor kinase 2	GRK3	*ADRBK2*, P35626	2.7.11.15	–
G protein-coupled receptor kinase 4	GRK4	*GRK4*, P32298	2.7.11.16	Inhibited by Ca^{2+}/calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158) [345]
G protein-coupled receptor kinase 5	GRK5	*GRK5*, P34947	2.7.11.16	Phosphorylated and inhibited by protein kinase C [344]
G protein-coupled receptor kinase 6	GRK6	*GRK6*, P43250	2.7.11.16	–
G protein-coupled receptor kinase 7	GRK7	*GRK7*, Q8WTQ7	2.7.11.14, 2.7.11.16	–

Comments: Loss-of-function mutations in GRK1 or retinal and pineal gland arrestin (*SAG*, P10523) are associated with Oguchi disease (OMIM: 181301), a form of congenital stationary night blindness.

Protein kinase A

Overview: Cyclic AMP-mediated signalling involves regulation of cyclic nucleotide-gated ion channels, members of the Rap guanine nucleotide exchange family (*Epac*, ENSFM00250000000899) and activation of protein kinase A (PKA, also known as cyclic AMP-dependent protein kinase). 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, [320]) by differential activation by N^6 benzyl-cAMP (see Table) and 8-pCPT-2′-O-Me-cAMP, respectively [337].

Nomenclature	protein kinase A
UniProtKB AC	–
EC number	2.7.11.11
Activators	N^6 benzyl-cAMP [315]
Inhibitors (pIC_{50})	Rp-cAMPS
Radioligands (K_d)	[^{3}H]cAMP (Activator)

Comments: Other members of the PKA family are PRKX (X-linked protein kinase, *PKX1*, P51817) and PRKY (Y-linked protein kinase, *PRKY*, O43930). PRKX and PRKY are expressed on X and Y chromosomes, respectively, and appear to interchange in some XX males and XY females [347].

Akt (Protein kinase B)

Overview: The action of phosphatidylinositol 3-kinase (PI3K), a downstream kinase activated by receptor tyrosine kinases, produces a series of phosphorylated phosphoinositides, which recruit 3-phosphoinositide-dependent kinase (*PDPK1*, O15530) activity to the plasma membrane, leading to activation of Akt (EC 2.7.11.11). Akt may be activated by PIP_3, PDK1-mediated phosphorylation [309] and mTORC2-mediated phosphorylation [331,346].

Nomenclature	v-akt murine thymoma viral oncogene homolog 1	v-akt murine thymoma viral oncogene homolog 2	v-akt murine thymoma viral oncogene homolog 3
Common abbreviation	Akt1	Akt2	AKT3
HGNC, UniProt	*AKT1*, P31749	*AKT2*, P31751	*AKT3*, Q9Y243
Selective inhibitors (pIC_{50})	GSK690693 [330]	–	–

Protein kinase C (PKC)

Overview: Protein kinase C (EC 2.7.11.13) is the target for the tumour-promoting phorbol esters, such as tetradecanoyl-β-phorbol acetate (TPA, also known as phorbol 12-myristate 13-acetate).

Classical protein kinase C isoforms: **PKCα, PKCβ, PKCγ.** Members of the classical protein kinase C family are activated by Ca^{2+} and diacylglycerol, and may be inhibited by GF109203X, calphostin C, Gö6983, chelerythrine and Ro318220.

Nomenclature	protein kinase C, alpha	protein kinase C, beta	protein kinase C, gamma
Common abbreviation	PKCα	PKCβ	PKCγ
HGNC, UniProt	*PRKCA*, P17252	*PRKCB*, P05771	*PRKCG*, P05129
Selective inhibitors (pIC_{50})	–	ruboxistaurin (8.3) [334], CGP53353 (6.4) [313]	–

Novel protein kinase C isoforms: **PKCδ, PKCε, PKCη, PKCθ and PKCμ.** Members of the novel protein kinase C family are activated by diacylglycerol and may be inhibited by calphostin C, Gö6983 and chelerythrine.

Nomenclature	protein kinase C, delta	protein kinase C, epsilon	protein kinase C, eta	protein kinase C, theta	protein kinase D1
Common abbreviation	PKCδ	PKCε	PKCη	PKCθ	PKD1
HGNC, UniProt	*PRKCD*, Q05655	*PRKCE*, Q02156	*PRKCH*, P24723	*PRKCQ*, Q04759	*PRKD1*, Q15139

Atypical protein kinase C isoforms

Nomenclature	protein kinase C, iota	protein kinase C, zeta
Common abbreviation	PKCι	PKCζ
HGNC, UniProt	*PRKCI*, P41743	*PRKCZ*, Q05513
Endogenous activators	–	arachidonic acid [343]
Comment	Known as PKCλ in rodents	–

Protein kinase G (PKG)

Overview: Cyclic GMP-dependent protein kinase (EC 2.7.11.12) is a dimeric enzyme activated by cGMP generated by particulate guanylyl cyclases or soluble guanylyl cyclases.

Nomenclature	Protein kinase G (PKG) 1	Protein kinase G (PKG) 2
Common abbreviation	PKG1	PKG2
HGNC, UniProt	*PRKG1*, Q13976	*PRKG2*, Q13237
EC number	2.7.11.12	2.7.11.12
Selective inhibitors (pIC_{50})	Rp-8-CPT-cGMPS [312]	–

Mitogen-activated protein kinases (MAP kinases)

Overview: MAP kinases (CMGC kinases, ENSF00000000137, EC 2.7.11.24) may be divided into three major families: ERK, JNK and p38 MAP kinases.

ERK may be activated by phosphorylation by the dual specificity mitogen-activated kinase kinases, *MAP2K1* (Q02750, also known as MEK1) and *MAP2K2* (P36507, also known as MEK2). The inhibitors PD98059 [308,322] and U0126 [323,325] act to inhibit these enzymes [319], and are used to inhibit ERK1 and ERK2.

Nomenclature	mitogen-activated protein kinase 1	mitogen-activated protein kinase 3
Common abbreviation	ERK2	ERK1
HGNC, UniProt	*MAPK1*, P28482	*MAPK3*, P27361

JNK may be activated by phosphorylation by the dual specificity mitogen-activated kinase kinases, *MAP2K4* (P45985, also known as JNKK1) and *MAP2K7* (O14733, also known as JNKK2).

Nomenclature	mitogen-activated protein kinase 8	mitogen-activated protein kinase 9	mitogen-activated protein kinase 10
Common abbreviation	JNK1	JNK2	JNK3
HGNC, UniProt	*MAPK8*, P45983	*MAPK9*, P45984	*MAPK10*, P53779
Selective inhibitors (pIC_{50})	SP600125 (7.4) [311]	SP600125 (7.4) [311]	SP600125 (7.05) [311]

p38 may be activated by phosphorylation by the dual specificity mitogen-activated kinase kinases, *MAP2K3* (P46734, also known as MEK3) and *MAP2K6* (P52564, also known as SAPKK3).

Nomenclature	mitogen-activated protein kinase 11	mitogen-activated protein kinase 12	mitogen-activated protein kinase 13	mitogen-activated protein kinase 14
Common abbreviation	p38β	p38γ	p38δ	p38α
HGNC, UniProt	*MAPK11*, Q15759	*MAPK12*, P53778	*MAPK13*, O15264	*MAPK14*, Q16539
Selective inhibitors (pIC_{50})	SB202190 [341], SB203580 (pK_i 7.0) [324]	–	–	SB203580 (pK_i 8.0) [324]

Rho kinase

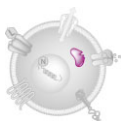
Overview: Rho kinase (also known as P160ROCK, Rho-activated kinase) is activated by members of the Rho small G protein family (ENSFM00500000269651), which are activated by GTP exchange factors, such as *ARHGEF1* (Q92888, p115-RhoGEF), which in turn may be activated by $G\alpha_{12/13}$ subunits [339].

Nomenclature	Systematic nomenclature	Common abbreviation	HGNC, UniProt	EC number	Selective inhibitors (pIC_{50})
Rho-associated, coiled-coil containing protein kinase 1	ROCK1	Rho kinase 1	*ROCK1*, Q13464	2.7.11.1	fasudil (Rabbit) [310], Y27632 (pK_i 6.9) [351]
Rho-associated, coiled-coil containing protein kinase 2	ROCK2	Rho kinase 2	*ROCK2*, O75116	2.7.11.1	fasudil (Rabbit) [310], Y27632 (pK_i 6.9) [351]

Other AGC kinases

Overview: For many of these remaining protein kinases, there is less information about the regulation and substrate specificity, as well as a paucity of pharmacological data

Nomenclature	Common abbreviation	HGNC, UniProt	EC number	Comment
dystrophia myotonica-protein kinase	DMPK1	*DMPK*, Q09013	2.7.11.1	Reduced expression of DMPK is associated with myotonic dystrophy 1 [336]
CDC42 binding protein kinase gamma (DMPK-like)	DMPK2	*CDC42BPG*, Q6DT37	2.7.11.1	–
CDC42 binding protein kinase alpha (DMPK-like)	MRCKα	*CDC42BPA*, Q5VT25	2.7.11.1	Reported to have a role in cellular iron regulation [317]
CDC42 binding protein kinase beta (DMPK-like)	MRCKβ	*CDC42BPB*, Q9Y5S2	2.7.11.1	Reported to be involved in cell migration [332]
citron (rho-interacting, serine/threonine kinase 21)	CRIK	*CIT*, O14578	2.7.11.1	Shares structural homology with the Rho kinases
Microtubule associated serine/threonine kinase 1	MAST1	*MAST1*, Q9Y2H9	2.7.11.1	Members of the microtubule-associated serine/threonine kinase family appear to have a role in platelet production [335] and inflammatory bowel disease [340]
Microtubule associated serine/threonine kinase 2	MAST2	*MAST2*, Q6P0Q8	2.7.11.1	See comment for MAST1
Microtubule associated serine/threonine kinase 3	MAST3	*MAST3*, O60307	2.7.11.1	See comment for MAST1
Microtubule associated serine/threonine kinase 4	MAST4	*MAST4*, O15021	2.7.11.1	See comment for MAST1
Microtubule associated serine/threonine kinase-like	MASTL	*MASTL*, Q96GX5	2.7.11.1	See comment for MAST1
large tumor suppressor kinase 1	LATS1	*LATS1*, O95835	2.7.11.1	The large tumour suppressor protein kinases are phosphorylated and activated by MST2 kinase (serine/threonine kinase 3, *STK3*, Q13188, [314])
large tumor suppressor kinase 2	LATS2	*LATS2*, Q9NRM7	2.7.11.1	See comment for LATS1
Serine/threonine kinase 38	NDR1	*STK38*, Q15208	2.7.11.1	–
Serine/threonine kinase 38 like	NDR2	*STK38L*, Q9Y2H1	2.7.11.1	–
3-phosphoinositide dependent protein kinase-1	PDK1	*PDPK1*, O15530	2.7.11.1	–
protein kinase N1	PKN1	*PKN1*, Q16512	2.7.11.13	PKN family members are activated by Rho, PIP_3 and PDK1 [321]
protein kinase N2	PKN2	*PKN2*, Q16513	2.7.11.13	See comment for PKN1
protein kinase N3	PKN3	*PKN3*, Q6P5Z2	2.7.11.13	See comment for PKN1
ribosomal protein S6 kinase, 90kDa, polypeptide 5	MSK1	*RPS6KA5*, O75582	2.7.11.1	The mitogen- and stress-acted protein kinases are activated by phosphorylation evoked by MAP kinases and appear to be central to that pathway of cAMP response element-binding protein phosphorylation [352]
ribosomal protein S6 kinase, 90kDa, polypeptide 4	MSK2	*RPS6KA4*, O75676	2.7.11.1	See comment for MSK1
ribosomal protein S6 kinase, 70kDa, polypeptide 1	p70S6K	*RPS6KB1*, P23443	2.7.11.1	Ribosomal S6 kinases 70 kDa, also known as $p70^{rsk}$, are activated by MAP kinase-mediated phosphorylation
ribosomal protein S6 kinase, 70kDa, polypeptide 2	p70S6Kβ	*RPS6KB2*, Q9UBS0	2.7.11.1	See comment for p70S6K
ribosomal protein S6 kinase, 90kDa, polypeptide 1	p90RSK	*RPS6KA1*, Q15418	2.7.11.1	Ribosomal S6 kinase 90 kDa serine/threonine kinases, also known as $p90^{rsk}$ or MAPK-activated protein kinase-1 (MAPKAP-K1), are activated by MAP kinase -mediated phosphorylation. RSK protein kinases are also activated by phosphorylation by TORC1 [327,338] and PDK1 [333]. Substrates include ribosomal S6 protein (RPS6, P62753), GS3β (P49841) [349]) and the $5HT_{2A}$ receptor [348]



Nomenclature	Common abbreviation	HGNC, UniProt	EC number	Comment
ribosomal protein S6 kinase, 90kDa, polypeptide 3	RSK2	*RPS6KA3*, P51812	2.7.11.1	see comment for p90RSK
ribosomal protein S6 kinase, 90kDa, polypeptide 2	RSK3	*RPS6KA2*, Q15349	2.7.11.1	see comment for p90RSK
ribosomal protein S6 kinase, 90kDa, polypeptide 6	RSK4	*RPS6KA6*, Q9UK32	2.7.11.1	see comment for p90RSK
SGK494	–	*SGK494*, Q96LW2	2.7.11.1	see comment for p90RSK
ribosomal protein S6 kinase, 52kDa, polypeptide 1	RSKL1	*RPS6KC1*, Q96S38	2.7.11.1	–
ribosomal protein S6 kinase-like 1	RSKL2	*RPS6KL1*, Q9Y6S9	2.7.11.1	–
serum/glucocorticoid regulated kinase 1	SGK1	*SGK1*, O00141	2.7.11.1	Serum- and glucocorticoid-inducible kinases are regulated at the transcriptional level by serum and glucocorticoids. SGK1 has been reported to be phosphorylated and activated by mouse TORC2 (Q3U182) [326]
serum/glucocorticoid regulated kinase 2	SGK2	*SGK2*, Q9HBY8	2.7.11.1	see comment for SGK1
serum/glucocorticoid regulated kinase family, member 3	SGK3	*SGK3*, Q96BR1	2.7.11.1	see comment for SGK1
serine/threonine kinase 32A	YANK1	*STK32A*, Q8WU08	2.7.11.1	–
serine/threonine kinase 32B	YANK2	*STK32B*, Q9NY57	2.7.11.1	–
serine/threonine kinase 32C	YANK3	*STK32C*, Q86UX6	2.7.11.1	–

Selected non-AGC protein kinase activities

Nomenclature	AMP kinase	Casein kinase 2	myosin light chain kinase	myosin light chain kinase 2	Calmodulin-dependent kinase II
Common abbreviation	AMPK	CK2	smMLCK	skMLCK	CaMKII
HGNC, UniProt	–	–	*MYLK*, Q15746	*MYLK2*, Q9H1R3	–
EC number	2.7.11.1	2.7.11.1	2.7.11.18	2.7.11.18	2.7.11.17
Endogenous activators	AMP	–	calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158) [329]	calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158) [329]	calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158)
Selective activators	AICA-riboside [318]	–	–	–	–
Selective inhibitors (pIC_{50})	dorsomorphin [355]	DRB [354]	–	–	K-252a [328]

Comments: AMP-activated protein kinase is a heterotrimeric protein kinase, made up of α, β and γ subunits, while casein kinase 2 is a heterotetrameric protein kinase, made up of 2 β subunits with two other subunits of α and/or α' composition. STO609 is an inhibitor of calmodulin kinase kinase (ENSFM00250000001201, [350]), an upstream activator of calmodulin-dependent kinase.

Further reading

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Sphingosine 1-phosphate turnover

Overview: S1P (sphingosine 1-phosphate) is a pro-survival signal, in contrast to ceramide. It is formed by the sphingosine kinase-catalysed phosphorylation of sphingosine. S1P can be released from cells to act as an agonist at a family of five G protein-coupled receptors ($S1P_{1\text{-}5}$) but also has intracellular targets. S1P can be dephosphorylated back to sphingosine or hydrolysed to form hexadecanal and phosphoethanolamine. Sphingosine choline phosphotransferase (EC 2.7.8.10) generates sphingosylphosphocholine from sphingosine and CDP-choline. Sphingosine β-galactosyltransferase (EC 2.4.1.23) generates psychosine from sphingosine in the presence of UDP-α-D-galactose. The molecular identities of these enzymes have not been confirmed.

Sphingosine kinase

Nomenclature	sphingosine kinase 1	sphingosine kinase 2
Common abbreviation	SPHK1	SPHK2
HGNC, UniProt	*SPHK1*, Q9NYA1	*SPHK2*, Q9NRA0
EC number	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP, sphinganine + ATP = sphinganine 1-phosphate + ADP	
Cofactors	Mg^{2+}	
(Sub)family-selective inhibitors	sphingosine kinase inhibitor [356]	
Selective inhibitors	PF-543 [361], SK1-I [360]	ABC294640 [357], ROMe [358]

Sphingosine 1-phosphate phosphatase

Nomenclature	sphingosine-1-phosphate phosphatase 1	sphingosine-1-phosphate phosphatase 2
Common abbreviation	SGPP1	SGPP2
HGNC, UniProt	*SGPP1*, Q9BX95	*SGPP2*, Q8IWX5
EC number	3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate	
Comment	Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [359]	–

Sphingosine 1-phosphate lyase

Nomenclature	HGNC, UniProt	EC number	Cofactors	Comment
sphingosine-1-phosphate lyase 1	*SGPL1*, O95470	4.1.2.27: sphinganine 1-phosphate -> phosphoethanolamine + hexadecanal	pyridoxal phosphate	THI (2-Acetyl-5-tetrahydroxybutyl imidazole) inhibits the enzyme activity in intact cell preparations [362]

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Thyroid hormone turnover

Overview: The thyroid hormones triiodothyronine and thyroxine, usually abbreviated as T_3 and T_4, respectively, are synthesized in the thyroid gland by sequential metabolism of tyrosine residues in the glycosylated homodimeric protein thyroglobulin (*TG*, P01266) under the influence of the haem-containing protein iodide peroxidase. Iodide peroxidase/TPO is a haem-containing enzyme, from the same structural family as eosinophil peroxidase (*EPX*, P11678), lactoperoxidase (LPO, P22079) and myeloperoxidase (MPO, P05164). Circulating thyroid hormone is bound to thyroxine-binding globulin (SERPINA7, P05543).

Nomenclature	thyroid peroxidase
Common abbreviation	TPO
HGNC, UniProt	*TPO*, P07202
EC number	1.11.1.8: [Thyroglobulin]-L-tyrosine + I^- + H_2O_2 + H^+ -> [Thyroglobulin]-3,5,3′-triiodo-L-thyronine + [thyroglobulin]-aminoacrylate + H_2O
Cofactors	Ca^{2+}
Selective inhibitors (pIC_{50})	methimazole [363], propylthiouracil [363]
Comment	Carbimazole is a pro-drug for methimazole

Tissue deiodinases These are 1 TM selenoproteins that remove an iodine from T_4 (3,3′,5,5′-tetraiodothyronine) to generate T_3 (3,3′,5-triiodothyronine, a more potent agonist at thyroid hormone receptors) or rT_3 (rT3, 3,3′,5′-triiodothyronine, a relatively inactive analogue). DIO1 is also able to deiodinate RT3 to form 3,3′-diiodothyronine (T_2). Iodotyrosine deiodinase is a 1TM homodimeric enzyme.

Nomenclature	deiodinase, iodothyronine, type I	deiodinase, iodothyronine, type II	deiodinase, iodothyronine, type III
Common abbreviation	DIO1	DIO2	DIO3
HGNC, UniProt	*DIO1*, P49895	*DIO2*, Q92813	*DIO3*, P55073
EC number	1.97.1.10: T_4 -> T_3, rT_3 -> T_2	1.97.1.10: T_4 -> T_3, rT_3 -> T_2	1.97.1.11: T_4 -> T_3, rT_3 -> T_2

Nomenclature	iodotyrosine deiodinase
Common abbreviation	IYD
HGNC, UniProt	*IYD*, Q6PHW0
EC number	1.22.1.1: 3-iodotyrosine -> L-tyrosine + I^-, 3,5-diiodo-L-tyrosine -> 3-iodotyrosine + I^-
Cofactors	NADPH, flavin adenine dinucleotide

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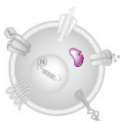

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