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.-- Transf erase s;
- 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 monophosphate 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.

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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

1799 Acetylcholine turnover
1800 Adenosine turnover
1801 Amino acid hydroxylases
1802 L-Arginine turnover
1803 Carboxylases and decarboxylases
1804 Catecholamine turnover
1810 Ceramide turnover
1815 Cyclic nucleotide turnover
1820 Cytochrome P450
1824 Eicosanoid turnover
1828 Endocannabinoid turnover
1830 GABA turnover
1832 Glycerophospholipid turnover
1838 Haem oxygenase
1839 Hydrogen sulfide synthesis
1840 Inositol phosphate turnover
1842 Lanosterol biosynthesis pathway
1845 Peptidases and proteinases
1853 Protein serine/threonine kinases
1860 Sphingosine 1-phosphate turnover
1862 Thyroid hormone turnover

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of Concise Guide: http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full
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, activating muscarinic acetylcholine receptors. In the latter, acetylcholine is involved as a neurotransmitter at the ganglion, activating nicotinic acetylcholine receptors. Acetylcholine is synthesised in neurons 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]) |
| acetylcholinesterase          | AChE                | ACHE, P22303 | 3.1.1.7: acetylcholine + H₂O = acetic acid + choline + H⁺                         |                                                                       |
| butyrylcholinesterase         | BChE                | BCHE, P06276 | 3.1.1.7: acetylcholine + H₂O = acetic acid + choline + H⁺                         |                                                                       |
| (Sub)family-selective inhibitors (pIC₅₀) |                      |              | physostigmine (7.6 – 7.8) [6]                                                      |                                                                       |
| Selective inhibitors (pIC₅₀)   | donepezil (7.7 – 8.1) [4,6], BW284C51 (7.7) [5] |              | physostigmine (7.6 – 7.8) [6]                                                      |                                                                       |
|                                | bambutrol (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].

Further reading

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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 PO₄³⁻). It is inactivated either by extracellular metabolism via adenosine deaminase (also producing NH₃) 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              | NTSE                 | SAHH                             |
| HGNC, UniProt                 | ADA, P00813         | ADK, PS5263      | NTSE, 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 | 5′-adenosine, guanine, inosine, uridine |
| Products                      | 2′-deoxyinosine, inosine | AMP            | αβ-methyleneADP (8.7) | 3-deazaadenosine (8.5) |
| Selective inhibitors (pIC₅₀)  | EHNA (pK 8.8) [8], pentostatin (10.8) [8] | A134974 (10.2) [14], ABT702 (8.8) [11] |                      |                                  |

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 (Q9UB4) deaminates transfer RNA; ADAR (EC 3.5.4.4, also known as 136 kDa double-stranded RNA-binding protein, P136, K88DSRB, Interferon-inducible protein 4); ADARB1 (EC 3.5.3.9, also known as dsRNA adenosine deaminase) and ADARB2 (EC 3.5.3.9, 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|
HGNC, UniProt          | PH, PAH, P00439             | TH, P07101              | TPH1, P17752              | TPH2, Q8IWWJ              |
| EC number           | 1.14.16.1: L-phenylalanine + O2 -> L-tyrosine | 1.14.16.2: L-tyrosine + O2 -> 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] |  |
| Endogenous substrates | L-phenylalanine | L-tyrosine | L-tryptophan | 5-hydroxy-L-tryptophan |
| Products            | L-tyrosine | L-DOPA | L-tryptophan | 5-hydroxy-L-tryptophan |
| Cofactors           | tetrahydrobiopterin | – | Fe^{2+}, tetrahydrobiopterin | – |
| Selective inhibitors (pIC_{50}) | α-methylphenylalanine [18], PCPA | – | 3-chlorotyrosine, 3-iodotyrosine, α-methylyrosine, α-propyldopacetamide | – |
| Inhibitors (pIC_{50}) | – | – | – | – |
| Comment             | PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monoxygenase 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.

**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 | ARGI, P05089 | ARG2, P78540 |

**Comments:** Nω-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 Nω-hydroxy-nor-L-arginine [34], S-(2-boronoethyl)-L-cysteine [25,30] and 2(S)-amino-6-boronohecanoic acid [23,25].

**Arginine: glycine amidinotransferase**

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

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Full Contents of Concise Guide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full)
Dimethylarginine dimethylaminohydrolases

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

| Nomenclature | $N^\gamma,N^\gamma$-Dimethylarginine dimethylaminohydrolase 1 | $N^\gamma,N^\gamma$-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$^\omega$propyl-L-arginine (pK 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$_2$O$_2$ 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\textsuperscript{2},N\textsuperscript{4}-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 | PRMT4, Q86X55 | PRMT5, O14744 | PRMT6, Q96LA8 | PRMT7, Q9NVM4 | PRMT8, FBXO11, Q9NR22 | PRMT9, Q86XK2 | PRMT10, Q6P2P2 |
| EC number    | –     | –     | 2.1.1.125 | –     | –     | 2.1.1.125 | –     | 2.1.1.125, 2.1.1.126 | –     | –     |

Further reading

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Carboxylases and decarboxylases

Carboxylases

Overview: The carboxylases allow the production of new carbon-carbon bonds by introducing HCO₃⁻ or CO₂ 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 | – | – |
| HGNC, UniProt | PC, P11498 | ACACA, Q13085 | ACACB, O00763 | – | GGCX |
| 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, PO₄⁻ | malonyl-CoA, ADP, PO₄⁻ | malonyl-CoA, ADP, PO₄⁻ | ADP, methylmalonyl-CoA, PO₄⁻ | carboxylglutamyl peptides |
| Cofactors | biotin | biotin | biotin | biotin | NADPH, vitamin K hydroquinone |
| Selective inhibitors (pIC₅₀) | – | 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 CO₂ 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 + CO₂ | 4.1.1.15: L-glutamic acid + H⁺ -> GABA + CO₂ | 4.1.1.15: L-glutamic acid + H⁺ -> GABA + CO₂ |
| Endogenous substrates | S-adenosyl methionine | L-arginine | L-tryptophan, L-DOPA, S-hydroxy-L-tryptophan | S-HT, dopamine | L-glutamic acid, L-aspartic acid |
| Products | S⁵-deoxyadenosyl-(3-aminopropyl) methylsulfonium | agmatine [43] | S-HT, dopamine | – | L-glutamic acid, L-aspartic acid |
| Cofactors | pyruvic acid | pyridoxal phosphate | pyridoxal phosphate | pyridoxal phosphate | pyridoxal phosphate |
Nomenclature

| Selective inhibitors (plC50) | SAM486A (8.0) [41] | L-Arginine decarboxylase | L-Aromatic amino-acid decarboxylase | Glutamic acid decarboxylase 1 | Glutamic acid decarboxylase 2 |
|----------------------------|-------------------|--------------------------|---------------------------------|------------------------|-------------------------|
| Common abbreviation        | HDC, P191113      | MALYCD, O95822           | 3-hydroxybenzylhydrazine, benserazide, carbidopa, L-o-methyl dopa | s-allylglycine | s-allylglycine |
| EC number                  | 4.1.1.22          | 4.1.1.9                  |                                |                        |                         |
| Endogenous substrates      | L-histidine       | malonyl-CoA              | L-ornithine                     | Ornithine decarboxylase | Phosphatidylserine decarboxylase |
| Products                   | histamine         | acetyl CoA               | putrescine                      | ODC                    | PSDC                    |
| Cofactors                  | pyridoxal phosphate | pyridoxal phosphate     | pyridoxal phosphate            | ODC, P11926            | PISD, Q9UG56            |
| Selective inhibitors (plC50) | AMA, FMH [37]    | –                        | –                               | 4.1.1.17               | 4.1.1.65                |
| 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 + CO2, Reaction 2: 5-hydroxy-L-tryptophan → 5-HT + CO2, Reaction 3: L-tryptophan → tryptamine + CO2 | 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) | |

**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 catecholamines 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 (pIC50) | Comment                                                                 |
|----------------------------------------|---------------------|---------------|------------------|-----------------------------|-----------------------|--------------|-----------------------|-----------------------------|--------------------------------------------------------------------------|
| L-Phenylalanine hydroxylase            | PH                  | PAH, P00439   | 1.14.16.1:       | 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-monoxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria |
| Tyrosine aminotransferase              | TAT                 | TAT, P17735   | 2.6.1.5:         | 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 |
| L-Aromatic amino-acid decarboxylase     | AADC                | DDC, P20711   | 4.1.1.28:        | L-tryptophan, L-DOPA, 5-hydroxy-L-tryptophan | S-HT, dopamine        | pyridoxal phosphate | 3-hydroxybenzylhydrazine, benzerazine, carbidopa, L-α-methyldopa | AADC is a homodimer, Reaction 1: L-DOPA -> dopamine + CO₂, Reaction 2: 5-hydroxy-L-tryptophan -> 5-HT + CO₂, Reaction 3: L-tryptophan -> tryptamine + CO₂ |
| Nomenclature                  | Common abbreviation | HGNC, UniProt  | EC number                        | Endogenous activators                                                                 | Endogenous substrates                  | Products          | Cofactors                        | Inhibitors (pIC<sub>50</sub>) | Comment                                                                                      |
|------------------------------|---------------------|----------------|----------------------------------|----------------------------------------------------------------------------------------|----------------------------------------|-------------------|----------------------------------|--------------------------------|---------------------------------------------------------------------------------------------|
| L-Tyrosine hydroxylase       | TH                  | TH, P07101     | 1.14.16.2: L-tyrosine + O<sub>2</sub> -> L-DOPA | Protein kinase A-mediated phosphorylation [51]                                           | L-tyrosine                             | L-DOPA            | Fe<sup>2+</sup>, tetrahydrobiopterin | 3-chloro tyrosine, 3-iodo tyrosine, α-methyl tyrosine, α-propyldopacetamide | TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [47] |
| Dopamine beta-hydroxylase    | DBH                 | DBH, P09172    | 1.14.17.1: dopamine + O<sub>2</sub> -> (-)-noradrenaline + H<sub>2</sub>O | Cu<sup>2+</sup>, L-ascorbic acid                                                        | nepicapstat                            |                   |                                  | [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] |
| Phenylethanolamine N-methyltransferase | PNMT               | PNMT, P11086   | 2.1.1.28: (-)-noradrenaline -> (-)-adrenaline | S-adenosyl methionine                                                                | LY134046 (pK 7.6) [48] |                   |                                  |                                           |                                                                 |
| Monoamine oxidase A          | MAO-A               | MAOA, P21397   | 1.4.3.4: dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH<sub>3</sub> | flavin adenine dinucleotide                                                      | befloxatone [46], clorgyline, pirlindole [53] |                   | Monoamine oxidase B             | MAO-B                                      |                                                                 |
|                              |                     |                | 1.4.3.4: dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH<sub>3</sub> | flavin adenine dinucleotide                                                      | lazabemide [50], L-Deprenyl, rasagiline [56] |                   | MAO8, P27338                     | 1.4.3.4: dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH<sub>3</sub> |                                                                 |
Catechol-O-methyltransferase (COMT) is an enzyme that catalyzes the transfer of a methanol group from S-adenosyl methionine to various substrates, including dopamine, noradrenaline, and adrenaline. This reaction is crucial in the metabolism of catecholamines.

**Cofactors and inhibitors**
- **Cofactors**: S-adenosyl methionine
- **Selective inhibitors** (pIC₅₀): entacapone [52,54], tolcapone [52,54]

**Comment**
- COMT exists in both membrane-bound and soluble forms.
- It methylates 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 myristoyl-CoA prominent for SPT1/SPT3/ssSPTa complexes, while SP1/SPT3/ssSPTb complexes had similar activity with C16, C18 and C20 acylCoAs [62].

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| 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 + CO₂ | pyridoxal phosphate + 3-Ketosphinganine + NADPH | pyridoxal phosphate + 3-Ketosphinganine + NADPH | serine palmitoyltransferase, small subunit A | serine palmitoyltransferase, small subunit B |
| Selective inhibitors (pIC₅₀) | 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, Q8NSB7 | 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 Δ⁴-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 + O₂ -> ceramide + H₂O + NAD, sphinganine + NADH + O₂ -> sphingosine + H₂O + 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 Δ⁴-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 | sterile alpha motif domain containing 8 |
|--------------|----------------------------------------|
| HGNC, UniProt | SAMD8, Q96LT4                          |
| EC number    | 2.7.8.-: ceramide + phosphatidylethanolamine -> ceramide phosphoethanolamine |

**Sphingomyelin phosphodiesterase**

**Overview:** Also known as sphingomyelinase.

| Nomenclature | sphingomyelin phosphodiesterase 1, acid lysosomal |
|--------------|---------------------------------------------------|
| HGNC, UniProt | SMPD1, P17405                                      |
| EC number    | 3.1.4.12: sphingomyelin -> ceramide + phosphocholine |

| Nomenclature | sphingomyelin phosphodiesterase 2, neutral membrane (neutral sphingomyelinase) |
|--------------|--------------------------------------------------------------------------------|
| HGNC, UniProt | SMPD2, O60906                                                                       |
| EC number    | 3.1.4.12: sphingomyelin -> ceramide + phosphocholine |

| Nomenclature | sphingomyelin phosphodiesterase 3, neutral membrane (neutral sphingomyelinase II) |
|--------------|--------------------------------------------------------------------------------|
| HGNC, UniProt | SMPD3, Q9NY59                                                                       |

| Nomenclature | sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3) |
|--------------|--------------------------------------------------------------------------------|
| HGNC, UniProt | SMPD4, Q9NXE4                                                                       |

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

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

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Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of Concise Guide: http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full
Neutral sphingomyelinase coupling factors

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

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

Comments: Two further structurally-related proteins have been identified (ASA2H2B, P0C7U1 and ASA2H2C, P0C7U2). ASA2H2B 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 optima 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          | EN, UniProt                      | EC number                       | Selective inhibitors (pIC50)     |
|-----------------------|----------------------------------|---------------------------------|---------------------------------|
| 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 Gαi (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:

| 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 | Gαi, Gq, Gβγ [133–134] | Gαi, RGS2 (RGS2, P41220), CaM kinase II-evoked phosphorylation [127,134,140] | Ca2+ [82] |

### Calmodulin-stimulated adenylyl cyclases

| Nomenclature | AC5 | AC6 | AC9 |
|--------------|-----|-----|-----|
| HGNC, UniProt| ADCY5, Q95622 | ADCY6, O43306 | ADCY9, O60503 |
| Endogenous activators | PKC-evoked phosphorylation [111] | - | - |
| Endogenous inhibitors | Gαi, Ca2+, PKA-evoked phosphorylation [108–109,134] | Gαi, Ca2+, PKA-evoked phosphorylation, PKC-evoked phosphorylation [87,112,134,141] | Ca2+ /calcineurin [120] |
| Selective inhibitors (pIC50) | NKY80 [119] | - | - |

### Calcium-inhibitable adenylyl cyclases

| Nomenclature | AC2 | AC4 | AC7 |
|--------------|-----|-----|-----|
| HGNC, UniProt| ADCY2, Q08462 | ADCY4, Q8NF4 | ADCY7, P51828 |
| Endogenous activators | Gβγ, PKC-evoked phosphorylation [85,114,133] | Gβγ [99] | PKC-evoked phosphorylation [139] |
| Endogenous inhibitors | - | - | - |
| Selective inhibitors (pIC50) | - | - | - |
NO has been proposed to inhibit AC5 and AC6 selectively [104], although it is unclear whether this phenomenon is of physiological significance. A soluble adenyl 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 (pIC50 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 (pIC50) | 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 (ENSFM002500000008999), which also includes RapGEF5 (GFR, KIAA0277, MR-GEF, Q92565) and RapGEL1 (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 (pIC50) | – | 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 IC50 value in the millimolar range for all isoforms except PDE 8A, 8B and 9A. A 2′,3′-cyclic nucleotide 3′-phosphodiesterase (E.C. 3.1.4.37 CNPase) activity is associated with myelin formation in the development of the CNS.
| Nomenclature | PDE1A | PDE1B | PDE1C |
|--------------|-------|-------|-------|
| 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 | cGMP (Selective) | cGMP (Selective) |
| Selective inhibitors (pIC\(_{50}\)) | – | 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 | – | cAMP >> cGMP | cAMP >> cGMP | cAMP >> cGMP |
| Rank order of affinity | cAMP >> cGMP | cAMP >> cGMP | cAMP >> cGMP | PKA-mediated phosphorylation [107] |
| 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 (8.1) [123], rolipram (6.5) [138], Ro201724 (6.4) [138] | rolipram (7.2) [138], Ro201724 (6.2) [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 \(^3H\)rolipram.
Nomenclature
HGNC, UniProt
EC number
Activators
Rank order of affinity
Selective inhibitors ($pIC_{50}$)

**PDE5A**

HGNC, UniProt: PDE5A, Q76074
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]

**PDE6A**

HGNC, UniProt: PDE6A, P16499
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cGMP > cAMP
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]

**PDE6B**

HGNC, UniProt: PDE6B, P35913
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cGMP > cAMP
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]

**PDE6C**

HGNC, UniProt: PDE6C, P51160
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cGMP > cAMP
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]

**PDE6D**

HGNC, UniProt: PDE6D, O43924
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cGMP > cAMP
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]

**PDE6G**

HGNC, UniProt: PDE6G, P18545
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cGMP > cAMP
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]

**PDE6H**

HGNC, UniProt: PDE6H, Q13956
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cGMP > cAMP
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]

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 (Gαt) 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
HGNC, UniProt
EC number
Rank order of affinity
Selective inhibitors ($pIC_{50}$)

**PDE7A**

HGNC, UniProt: PDE7A, Q13946
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cAMP >> cGMP [115]
Selective inhibitors ($pIC_{50}$): BRL50481 (6.7 – 6.8) [78,128]
Comment: PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively

**PDE7B**

HGNC, UniProt: PDE7B, Q9NP56
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cAMP >> cGMP [100]
Selective inhibitors ($pIC_{50}$): dipyridamole (5.7 – 6.0) [100,124], SCH51866 (5.8) [124], BRL50481 (4.9) [78]

**PDE8A**

HGNC, UniProt: PDE8A, O60658
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cAMP >> cGMP [93]
Selective inhibitors ($pIC_{50}$): dipyridamole (5.1) [93]

**PDE8B**

HGNC, UniProt: PDE8B, Q95263
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cAMP >> cGMP [102]
Selective inhibitors ($pIC_{50}$): dipyridamole (4.3) [102]

**PDE9A**

HGNC, UniProt: PDE9A, Q76083
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cGMP >> cAMP [94]
Selective inhibitors ($pIC_{50}$): SCH51866 (5.8) [94], zaprinast (4.5) [94]

**PDE10A**

HGNC, UniProt: PDE10A, Q9Y233
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cAMP, cGMP [97]
Selective inhibitors ($pIC_{50}$): cAMP, cGMP [91]

**PDE11A**

HGNC, UniProt: PDE11A, Q9HCR9
EC number: 3.1.4.17
Activators: α-subunit of transducin (Gαt)
Rank order of affinity: cAMP, cGMP [91]
Selective inhibitors ($pIC_{50}$): 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 monoxygenases 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 congenital glaucoma [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, Q6VX0| 1.14.13.15 | Converts vitamin D₃ to 25-hydroxyvitamin D₃ [146] |
| CYP2S1       | CYP2S1, Q96SQ9| 1.14.14.1 |         |

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Full Contents of Concise Guide: http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full
### Nomenclature HGNC, UniProt EC number Comment

| 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 | 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, QSTCH4   | 1.14.15.3                  | –                                            |
| CYP4B1       | CYP4B1, P13584    | 1.14.14.1                  | –                                            |
| CYP4F2       | CYP4F2, P78329    | 1.14.13.30                 | Responsible for ω-hydroxylation of LTβs, LXβs [155], and tocopherols, including vitamin E [163] | Responsible for ω-hydroxylation of LTβs, LXβs [155], and polyunsaturated fatty acids [147,151] |
| CYP4F3       | CYP4F3, Q08477    | 1.14.13.30                 | Converts PGH₂ to 19-hydroxyPGH₂ [145] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [157] | Converts PGH₂ to 19-hydroxyPGH₂ [145] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [157] |
| CYP4F8       | CYP4F8, P98187    | 1.14.14.1                  | –                                            |
| CYP4F11      | CYP4F11, Q9HB16   | 1.14.14.1                  | –                                            |
| CYP4F12      | CYP4F12, Q9HC52   | 1.14.14.1                  | AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12 | Converts arachidonic acid to 16-HETE and 18-HETE [157] |
| CYP4F22      | CYP4F22, Q6NT55   | 1.14.14.-                  | Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [164] | Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [164] |
| CYP4V2       | CYP4V2, Q6ZW1L    | 1.14.-                      | Converts myristic acid to 14-hydroxymyristic acid [156] | Converts myristic acid to 14-hydroxymyristic acid [156] |
| CYP4X1       | CYP4X1, Q8N118    | 1.14.14.1                  | Converts lauric acid to 12-hydroxylauric acid | Converts lauric acid to 12-hydroxylauric acid |
| CYP4Z1       | CYP4Z1, Q8W610    | 1.14.14.1                  | –                                            |
### CYP5, CYP7 and CYP8 families

| Nomenclature | Common name                  | HGNC, UniProt   | EC number  | Comment                                                                                                                                 |
|--------------|------------------------------|----------------|------------|----------------------------------------------------------------------------------------------------------------------------------------|
| CYP5A1       | –                            | TBXAS1, P24557 5.3.99.5 | Converts PGH2 to thromboxane A2. Inhibited by dazoxiben [161] and camonagrel [150]                                                  |
| CYP8A1       | Prostacyclin synthase        | PTGIS, Q16647 5.3.99.4 | Converts prostaglandin H2 to prostaglandin I2 [152]. Inhibited by tranylcyromine [149]                                        |
| CYP7A1       | –                            | CYP7A1, P22680 1.14.13.17 | Converts cholesterol to 7α-hydroxycholesterol [158]                                                                                  |
| CYP7B1       | –                            | CYP7B1, Q75881 1.14.13.100 | Converts DHEA to 7α-DHEA [162]                                                                                                         |
| CYP8B1       | –                            | CYP8B1, Q9UNU6 1.14.13.95 | Converts 7α-hydroxycholester-4-en-3-one to 7-alpha,12α-dihydroxycholester-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 deoxycorticosterone 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-hydroxyprogrenolone and 17α-hydroxyprogesterone, respectively. Converts 17α-hydroxyprogrenolone and 17α-hydroxyprogesterone to dehydroepiandrosterone and androstenedione, respectively. Converts corticosterone to cortisol. Inhibited by abiraterone (pIC50 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 deoxycorticosterone and 11-deoxycortisol, respectively                  |

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**Full Contents of Concise Guide**: [http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full)
CYP24, CYP26 and CYP27 families

| Nomenclature | Common name | HGNC, UniProt | EC number | Comment |
|--------------|-------------|---------------|-----------|---------|
| CYP24A1      | –           | CYP24A1, Q07973 | 1.14.13.126 | Converts 1α,25-dihydroxyvitamin D₃ (calcitriol) to 1α,24R,25-trihydroxyvitamin D₃ |
| CYP26A1      | –           | CYP26A1, O43174 | 1.14.13.13 | Converts retinoic acid to 4-hydroxyretinoic acid. Inhibited by liarozole |
| CYP26B1      | –           | CYP26B1, Q9NR63 | 1.14.13.13 | Converts retinoic acid to 4-hydroxyretinoic acid |
| CYP26C1      | –           | CYP26C1, Q6VOL0 | 1.14.13.13 | – |
| CYP27A1      | Sterol 27-hydroxylase | CYP27A1, Q02318 | 1.14.13.15 | Converts cholesterol to 27-hydroxysterol |
| CYP27B1      | –           | CYP27B1, O15528 | 1.14.13.13 | Converts 25-hydroxyvitamin D₃ to 1α,25-dihydroxyvitamin D₃ (calcitriol) |
| CYP27C1      | –           | CYP27C1, Q4G054 | 1.14.13.13 | – |

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 | 1.14.13.98 | Converts lanosterol to 4,4-dimethylcholesta-8,14-trienol |

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Full Contents of Concise Guide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full)
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 PGG2 from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH2 from PGG2. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indomethacin and paracetamol (acetaminophen). PGH2 may then be metabolised to prostaglandins and thromboxanes by various prostaglandin synthases in an apparently tissue-dependent manner.

Prostaglandin synthases

Overview: Subsequent to the formation of PGH2, the cytochrome P450 activities thromboxane synthase (CYP5A1, TRXAS1, P24557, EC 5.3.99.5) and prostacyclin synthase (CYP8A1, PTGIS, Q16647, EC 5.3.99.4) generate thromboxane A2 and prostacyclin (PGI2), respectively. Additionally, multiple enzyme activities are able to generate prostaglandin E2 (PGE2), prostaglandin D2 (PGD2) and prostaglandin F2α (PGF2α). PGD2 can be metabolised to 9α,11β-prostacyclin F2α through the multifunctional enzyme activity of AKR1C3. PGE2 can be metabolised to 9α,11β-prostacyclin F2α through the 9-ketoreductase activity of CBR1. Conversion of the 15-hydroxyeicosanoids, 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 (pIC50) | Comment |
|--------------|--------------|-----------|----------|-----------|----------------------------|---------|
| mPGES1       | PTGES, O14684| 5.3.99.3  | PGH2 => PGE2 | glutathione [175] | –                          | –       |
| mPGES2       | PTGES2, Q9H7Z7| 5.3.99.3  | PGH2 => PGE2 | Thiols, including dihydrolipoic acid [191] | –            | –       |
| cPGES        | PTGES3, Q15185| 5.3.99.3  | PGH2 => PGE2 | –                | –                          | 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  | PGH2 => PGD2 | – | – | – |
| H-PGDS       | HPGDS, O60760| 5.3.99.2  | PGH2 => PGD2 | HQL-79 (5.3 – 5.5) [169] | – |

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Full Contents of Concise Guide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full)
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
- **15-LOX-1**: ALOX15, P16050
- **15-LOX-2**: ALOX15B, O15296
- **E-LOX**: ALOX3, Q9BY1

**EC number**: 1.13.13.33 1.13.11.33 1.13.11.11

- **Endogenous substrates**: arachidonic acid + O2 \(\Rightarrow\) 15S-HPETE
- **Reaction 1**: arachidonic acid + O2 \(\Rightarrow\) 15S-HPETE
- **Reaction 2**: linoleic acid + O2 \(\Rightarrow\) 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.

### Leukotriene and lipoxin metabolism

#### Overview
Leukotriene A₄ (LTA₄), 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 LTA₄ at the 6 position with reduced glutathione to generate LTC₄ occurs under the influence of leukotriene C₄ synthase, with the subsequent formation of LTD₄ and LTE₄, all of which are agonists at CysLT receptors. LTD₄ formation is catalysed by γ-glutamyltransferase, and subsequently dipeptidase 2 removes the terminal glycine from LTD₄ to generate LTE₄. Leukotriene A₄ hydrolyase converts the 5,6-epoxide LTA₄ to the 5-hydroxylated LTB₄, an agonist for BLT receptors. LTA₄ is also acted upon by 12S-LOX to produce the trihydroxyeicosatetraenoic acids lipoxins LXA₄ and LXB₄. Treatment with a LTA₄ hydrolase inhibitor in a murine model of allergic airway inflammation increased LXA₄ levels, in addition to reducing LTB₄, in lung lavage fluid [186].

LTA₄ 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 LTA₄ hydrolase converted chiral S(6)-epoxide-containing intermediates to resolvin E1 and 18S-resolvin E1 [184].

#### Nomenclature
- **Leukotriene C₄ synthase**: LTC₄S, Q16873
- **γ-Glutamyltransferase**: GCCT, O75223
- **Dipeptidase 1**: DPEP1, P16444
- **Dipeptidase 2**: DPEP2, Q9H4A9
- **LTA₄ hydrolase**: LTA4H, P09960

**EC number**: 4.4.1.20 2.3.2.2 3.4.13.19 3.3.2.6

- **Reaction**: LTA₄ + glutathione \(\Rightarrow\) LTC₄
- **Inhibitors**: LTA₄, bestatin [185]

**Comment**: LTA₄ hydrolase is a member of a family of arginyl aminopeptidases (ENSFM0025000001675), which also includes aminopeptidase B (RNPEP, Q9HAU8). Dipeptidase 1 and 2 are members of a family of membrane dipeptidases (ENSFM0025000000170), which also includes (DPEP3, Q9H4B8) for which LTD₄ appears not to be a substrate.
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Endocannabinoid turnover

Overview: The principle endocannabinoids are 2-arachidonoylglycerol (2AG) and anandamide (N-arachidonoyl ethanolamine, 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 monooacylglycerol 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 | Monoacylglycerol lipase | DGLα | 3.1.1.23 | [201] |
| HGNC, UniProt | DAGLA | DAGLB, Q8NCQ7 | 3.1.1.23 | – |
| EC number | RHC80267, orlistat (7.2) [196] | RHC80267, orlistat (7.0) [196] | – | – |

| Nomenclature | N-Acylphosphatidylethanolamine-phospholipase D | NAPE-PLD | NAPEPLD, Q6IQA0 |
| HGNC, UniProt | DAGLA | DAGLB, Q8NCQ7 | Q6IQA0 |
| EC number | – | – | – |

| Selective inhibitors (pIC50) | RHC80267, orlistat (7.2) [196] | RHC80267, orlistat (7.0) [196] | – | – |

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.

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GABA turnover

Overview: The inhibitory neurotransmitter γ-aminobutyrate (GABA, 4-aminobutyrate) is generated in neurons 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 GABAA or GABAB 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 + CO₂ | |
| Endogenous substrates | L-glutamic acid, L-aspartic acid | |
| Products | GABA | |
| Cofactors | pyridoxal phosphate | |
| Selective inhibitors (pIC₅₀) | 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 + H₂O = 4-trimethylammoniobutanoate + NADPH + 2 H⁺, 1.2.1.3: an aldehyde + H₂O + NAD = a carboxylate + 2 H⁺ + NADH, 1.2.1.19: 4-aminobutanal + NAD + H₂O = 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 (pIC₅₀) | 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 + H₂O = succinic acid + NADH + 2 H⁺, 4-hydroxy-trans-2-nonenal + NAD + H₂O = 4-hydroxy-trans-2-nonoate + 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-$\beta$ 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-$\gamma$ involves their phosphorylation by receptor tyrosine kinases (RTK) in response to activation of a variety of growth factor receptors and immune system receptors. PLC-$\epsilon$ 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-$\delta$ 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 | PLC-$\beta$1 | PLC-$\beta$2 | PLC-$\beta$3 | PLC-$\beta$4 |
|--------------|-------------|-------------|-------------|-------------|
| HGNC, UniProt | PLCB1, Q9NQ66 | PLCB2, Q00722 | PLCB3, Q01970 | PLCB4, Q15147 |
| Endogenous activators | G$\alpha$q, G$\alpha$11, G$\beta$$\gamma$ | G$\alpha$16, G$\beta$$\gamma$, Rac2 (RAC2, P15153) | G$\alpha$q, G$\beta$$\gamma$ | G$\alpha$q |
| Endogenous inhibitors | – | – | – | – |

| Nomenclature | PLC-$\gamma$1 | PLC-$\gamma$2 | PLC-$\delta$1 | PLC-$\delta$3 | PLC-$\delta$4 |
|--------------|-------------|-------------|-------------|-------------|-------------|
| HGNC, UniProt | PLCG1, P19174 | PLCG2, P16885 | PLCD1, P51178 | PLCD3, Q8N3E9 | PLCD4, Q98RC7 |
| Endogenous activators | PIP$_2$, Rac1 (RAC1, P63000), Rac2 (RAC2, P15153), Rac3 (RAC3, P60763) | [217,251,243,246,228-231,247,249] | Transglutaminase II, p122-RhoGAP, spermine, G$\beta$$\gamma$ | [225,229,244,248] | – |
| Endogenous inhibitors | – | – | – | – | – |

| Nomenclature | PLC-$\epsilon$1 | PLC-$\zeta$1 | PLC-$\eta$1 | PLC-$\eta$2 |
|--------------|-------------|-------------|-------------|-------------|
| HGNC, UniProt | PLCCL1, Q15111 | PLCZ1, Q86YW0 | PLCH1, Q4KWH8 | PLCH2, Q75038 |
| Endogenous activators | Ras, rho [259,264] | – | – | G$\beta$$\gamma$ [266] |

**Comments:** A series of PLC-like proteins ($PLCL1$, Q15111; $PLCL2$, Q9UPR0 and $PLCH1$, Q4KWH8) form a family with PLC-$\delta$ and PLC-$\zeta$ isoforms, but appear to lack catalytic activity. PLC-$\delta$2 has been cloned from bovine sources [242].

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Phospholipase A₂

**Overview:** Phospholipase A₂ (PLA₂, 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 A₂ enzymes or have activity against other eicosanoid-metabolising enzymes.

### Secreted or extracellular forms:

| Nomenclature | sPLA₂-1B | sPLA₂-2A | sPLA₂-2D | sPLA₂-2E | sPLA₂-2F | sPLA₂-3 | sPLA₂-10 | sPLA₂-12A |
|--------------|---------|---------|---------|---------|---------|---------|---------|---------|
| HGNC, UniProt | PLA2G1B, P04054 | PLA2G2A, P14555 | PLA2G2D, Q9UNK4 | PLA2G2E, Q9N9K7 | PLA2G2F, Q9BZM2 | PLA2G3, Q9NZ20 | PLA2G10, O15496 | PLA2G12A, Q9BZM1 |

Cytosolic, calcium-dependent forms

| Nomenclature | cPLA₂-4A | cPLA₂-4B | cPLA₂-4C | cPLA₂-4D | cPLA₂-4E | cPLA₂-4F |
|--------------|---------|---------|---------|---------|---------|---------|
| HGNC, UniProt | PLA2G4A, P47712 | PLA2G4B, P0C869 | PLA2G4C, Q9UP65 | PLA2G4D, Q86XP0 | PLA2G4E, Q3MJ16 | PLA2G4F, Q68DD2 |

**Comment:** cPLA₂-4A also expresses lysophospholipase (EC 3.1.1.5) activity [256].

Other forms

| Nomenclature | PLA₂-G5 | iPLA₂-G6 | PLA₂-G7 | platelet-activating factor acetylhydrolase 2, 40kDa |
|--------------|---------|---------|---------|--------------------------------------------------|
| HGNC, UniProt | PLA2G5, P39877 | PLA2G6, O60733 | PLA2G7, Q13093 | PFAH2, Q99487 |
| Comment      | –       | –       | –       | PFAH2 also expresses PAF hydrolase activity (EC 3.1.1.47) |

**Comments:** The sequence of PLA₂-2C suggests a lack of catalytic activity, while PLA₂-12B (GXIIB, GXIII sPLA₂-like) appears to be catalytically inactive [254]. A further fragment has been identified with sequence similarities to Group II PLA₂ members. Otoconin 90 (OC90) shows sequence homology to PLA₂-G10. A binding protein for secretory phospholipase A₂ has been identified which shows modest selectivity for sPLA₂-1B over sPLA₂-2A, and also binds snake toxin phospholipase A₂ [216]. The binding protein appears to have clearance function for circulating secretory phospholipase A₂, as well as signalling functions, and is a candidate antigen for idiopathic membraneous nephropathy [219]. PLA₂-G7 and PFAH2 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 transphophatidylation reaction [253].

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Nomenclature PLD1 PLD2
HGNC, UniProt PLD1, Q13393 PLD2, Q14939
Endogenous activators Arf1 (ARF1, P84077), PIP2, RhoA, PKC evoked phosphorylation, RalA [226,241]
Endogenous inhibitor Gβγ [252]
Selective inhibitors (pIC50) – VU0364739 (7.7) [236]

Comments: A lysophospholipase D activity (ENPP2, Q13822, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2, phosphodiesterase I, nucleotide pyrophosphatase, autotaxin) has been described, which not only catalyses the production of lysophosphaticidic 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 transphosphatidylylate 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 phosphatic acid phosphatases or lipins catalyse the dephosphorylation of phosphatic acid (and other phosphorylated lipid derivatives) to generate inorganic PO4 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-P3 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 Lipin2
HGNC, UniProt LPIN1, Q14693 LPIN2, Q92539 LPIN3, Q9BQK8 PPA2A, P14494 PPA2B, O14495 PPA3A, Q43688
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
Substrates phosphatic acid phosphatic acid – phosphatic acid phosphatic acid – phosphatic acid
Phosphatidylinositol 3-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                                      | Common abbreviation | HGNC, UniProt     | EC number          | Selective inhibitors (pIC<sub>50</sub>) | Selective inhibitors (pIC<sub>50</sub>) |
|--------------------------------------------------|---------------------|-------------------|--------------------|---------------------------------------|---------------------------------------|
| Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha | p110α/PIK3CA        | PIK3CA, P42336    | 2.7.1.153, 2.7.11.1 | –                                     | –                                     |
| Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit beta   | p110β/PIK3CB        | PIK3CB, P42338    | 2.7.1.153          | –                                     | –                                     |
| Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta  | p110δ/PIK3CD        | PIK3CD, O00329    | 2.7.1.153          | –                                     | –                                     |
| Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit gamma  | p110γ/PIK3CG        | PIK3CG, P48736    | 2.7.1.153          | –                                     | –                                     |

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                                      | Common abbreviation | HGNC, UniProt     | EC number          | Selective inhibitors (pIC<sub>50</sub>) | Selective inhibitors (pIC<sub>50</sub>) |
|--------------------------------------------------|---------------------|-------------------|--------------------|---------------------------------------|---------------------------------------|
| Phosphoinositide-3-kinase, regulatory subunit 1 (alpha) | p85α/PIK3R1        | PIK3R1, P27986    | 2.7.1.154          | –                                     | –                                     |
| Phosphoinositide-3-kinase, regulatory subunit 2 (beta)   | p85β/PIK3R2        | PIK3R2, Q92569    | 2.7.1.154          | –                                     | –                                     |
| Phosphoinositide-3-kinase, regulatory subunit 3 (gamma)  | p85γ/PIK3R3        | PIK3R3, Q99570    | 2.7.11.1           | –                                     | –                                     |

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                                      | Common abbreviation | HGNC, UniProt     | EC number          | Selective inhibitors (pIC<sub>50</sub>) | Selective inhibitors (pIC<sub>50</sub>) |
|--------------------------------------------------|---------------------|-------------------|--------------------|---------------------------------------|---------------------------------------|
| Phosphatidylinositol 4-phosphate 3-kinase, catalytic subunit type 2 alpha | C2α/PIK3C2A         | PIK3C2A, O00443   | 2.7.1.154          | –                                     | –                                     |
| Phosphatidylinositol 4-phosphate 3-kinase, catalytic subunit type 2 beta   | C2β/PIK3C2B        | PIK3C2B, O00750   | 2.7.1.154          | –                                     | –                                     |
| Phosphatidylinositol 4-phosphate 3-kinase, catalytic subunit type 2 gamma  | C2γ/PIK3C2G        | PIK3C2G, O75747   | 2.7.1.154          | –                                     | –                                     |

**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.

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**Full Contents of Concise Guide:** [http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full)
| 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                                                       | PI4KIIA/PI4K4CA                               | PI4KIIA/PI4K4CB                                | PI4KIIA/PI4K2A                          | PI4KIIA/PI4K2B                          |
| HGNC, UniProt                                                              | PI4KA, P42356                                 | PI4KB, Q9UF8                                   | PI4K2A, Q9BTU6                          | PI4K2B, Q8TCG2                          |
| Endogenous activation                                                      |                                               |                                               |                                         |                                         |
| (Sub)family-selective inhibitors (pIC50)                                   | 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 (pIC50)                                               |                                               |                                               |                                         |                                         |

**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                                                   | PIP5K18, Q99755                                        | PIP5K1C, O60331                                         |
| HGNC, UniProt                                                              |                                                            | O14986                                                 |                                                        |
| 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, P78356                                        | PIP4K2G, Q8TBX8                                         |
| HGNC, UniProt                                                              |                                                            |                                                        |                                                        |
| 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 IC₅₀ 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           | CCB1, 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, NH₃, pyruvic acid | L-cysteine, NH₃, pyruvic acid | 3-mercaptopyruvic acid (Km 1.2x10⁻³ M) [270] |
| Products                      | cystathionine            | NH₃, pyruvic acid     | pyridoxal phosphate                      | pyruvic acid                        |
| Cofactors                     | pyridoxal phosphate      | propargylglycine      |                                          | Zn²⁺                                 |
| Inhibitors (pIC₅₀)            | aminooxyacetic acid      |                       |                                          |                                     |

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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 phosphatidylinositol synthase activity (CDP-diacylglycerol-inositol 3-phosphatidytransferase [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, ENSFM0025000001260) 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, ENSFM0025000001432) 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, Q81968; 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, 3.1.3.36, 3.1.3.36, 3.1.3.36, 3.1.3.36, 3.1.3.36, 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 hydrolysates myo-inositol monophosphate to generate myo-inositol and PO$_4$$^-$. glycerol may be a physiological phosphate acceptor. lithium is a nonselective un-competitive inhibitor more potent at IMPase 1 (pK$_{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, 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 | myo-inositol 4-phosphate > myo-inositol 3-phosphate > myo-inositol 1-phosphate [274] | – |

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Full Contents of Concise Guide: http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full
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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### 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

| Nomenclature | HGNC, UniProt | EC number | Comment |
|--------------|--------------|-----------|---------|
| acetyl-CoA acetyltransferase 1 | ACAT1, P24752 | 2.3.1.9: acetyl-CoA + acetyl-CoA = acetoacetyl-CoA + coenzyme A | |
| acetyl-CoA acetyltransferase 2 | ACAT2, Q9BWD1 | 2.3.1.9: acetyl-CoA + acetyl-CoA = acetoacetyl-CoA + coenzyme A | |
| hydroxymethylglutaryl-CoA synthase 1 | HMGCS1, Q01581 | 2.3.3.10: acetyl-CoA + H₂O + acetoacetyl-CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A | HMGCoA synthase is found in cytosolic and mitochondrial versions; the former associated with (R)-mevalonate synthesis and the latter with ketogenesis. |
| hydroxymethylglutaryl-CoA synthase 2 | HMGCS2, P54868 | 2.3.3.10: acetyl-CoA + H₂O + acetoacetyl-CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A | |
| hydroxymethylglutaryl-CoA reductase | HMGCR, P04035 | 1.1.1.34: (S)-3-hydroxy-3-methylglutaryl-CoA + NADPH -> (R)-mevalonate + coenzyme A + NADP⁺ | 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. |
| mevalonate kinase | MVK, Q03426 | 2.7.1.36: ATP + (R)-mevalonate -> ADP + (R)-5-phosphomevalonate | Mevalonate kinase activity is regulated by the downstream products farnesyl diphosphate and geranyl diphosphate as an example of feedback inhibition. |

Selective inhibitors (pIC₅₀)
- lovastatin (Competitive) (pKᵢ 9.22) [280]
- rosuvastatin (Competitive) (8.3) [283]
- atorvastatin (Competitive) (8.1) [283]
- simvastatin (Competitive) (7.96) [283]
- fluvastatin (Competitive) (7.55) [283]
| Nomenclature                  | Enzyme Name                                      |
|------------------------------|--------------------------------------------------|
| phosphomevalonate kinase     | PMVK, Q15126                                     |
| diphosphomevalonate decarboxylase | MVD, P53602                                    |
| isopentenyl-diphosphate Δ-isomerase 1 | IDI1, Q13907                                |
| isopentenyl-diphosphate Δ-isomerase 2 | IDI2, Q98X51                                  |
| geranylgeranyl diphosphate synthase | GGPS1, O95749                                    |
| farnesyl diphosphate synthase | FDPS, P14324                                     |
| squalene synthase            | FDT71, P37268                                    |

| EC number | Equation                                                                   |
|-----------|---------------------------------------------------------------------------|
| 2.7.4.2   | $\text{ATP} + (R)-5\text{-phosphomevalonate} \rightarrow \text{ADP} + (R)-5\text{-diphosphomevalonate}$ |
| 4.1.1.33  | $\text{ATP} + (R)-5\text{-diphosphomevalonate} \rightarrow \text{ADP} + \text{isopentenyl diphosphate} + \text{PO}_4^+ + \text{CO}_2$ |
| 5.3.3.2   | $\text{isopentenyl diphasphate} = \text{dimethylallyl diphasphate}$       |
| 2.5.1.10  | $\text{2.5.1.10: geranyl diphasphate} + \text{isopentenyl diphasphate} \rightarrow$ |
| 2.5.1.29  | $\text{trans,trans-farnesyl diphasphate} + \text{isopentenyl diphasphate} \rightarrow$ |
| 2.5.1.1   | $\text{2.5.1.1: dimethylallyl diphasphate} + \text{isopentenyl diphasphate} = \text{geranyl diphasphate} + \text{diphosphate ion}$ |
| 2.5.1.10  | $\text{2.5.1.10: geranyl diphasphate} + \text{isopentenyl diphasphate} \rightarrow$ |
| 2.5.1.29  | $\text{trans,trans-farnesyl diphasphate} + \text{isopentenyl diphasphate} \rightarrow$ |

Selective inhibitors (pIC₅₀):
- Risedronate (8.4) [281], Alendronate (6.34) [281]
- Zaragozic acid A (pKᵢ 10.1 - Rat) [282], FTI 276 (9.3) [284], Zaragozic acid A (9.15) [286]
Further reading

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Rozman D, Monostory K. (2010) Perspectives of the non-statin hypolipidemic agents. *Pharmacol Ther* 127: 19–40. [PMID:20420853]

Seiki S, Frishman WH. (2009) Pharmacologic inhibition of squalene synthase and other downstream enzymes of the cholesterol synthesis pathway: a new therapeutic approach to treatment of hypercholesterolemia. *Cardiol Rev* 17: 70–76. [PMID:19367148]
### Overview: Peptidases and Proteinases

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, (EC. 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 proteolyzed to form the mature protein. Members of the mammalian inhibitors of apoptosis proteins (IAP) are able to bind the pro-caspases, 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 | – |
| Activators | – | – | PAC1 [301], PETCM [295] | – |
| Selective inhibitors (pIC50) | Z-YVAD-FMK [287] | Z-VDVAD-FMK [291] | AZ10417808 [303], Z-DEVD-FMK [288], Z-DQMD-FMK [294] | Consists of caspase-4 subunit 1 and caspase-4 subunit 2 (see Uniprot entry) |
| 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 (pIC50) | Z-WEHD-FMK [299] | Z-VEID-FMK [302] | 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) |
| 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) | – |
**Nomenclature**
- Caspase 9
  - HGNC, UniProt: CASP9, P55211
  - EC number: 3.4.22.62
  - Endogenous activators: –
  - Endogenous substrates: caspase 9, PARP, pro-caspase 3, pro-caspase 6, pro-caspase 7
  - Selective inhibitors (pIC\textsubscript{50}): Z-LEHD-FMK [298]
  - Comment: Consists of caspase-9 subunit p35 and caspase-9 subunit p10 (see Uniprot entry)

- Caspase 10
  - HGNC, UniProt: CASP10, Q92851
  - EC number: 3.4.22.63
  - DISC
  - Endogenous substrates: caspase 10, pro-caspase 3, pro-caspase 6, pro-caspase 7
  - Selective inhibitors (pIC\textsubscript{50}): –
  - Comment: Consists of caspase-10 subunit p23/17 and caspase-10 subunit p12 (see Uniprot entry)

- Caspase 14
  - HGNC, UniProt: CASP14, P31944
  - EC number: 3.4.22.-
  - Endogenous activators: –
  - Endogenous substrates: –
  - Selective inhibitors (pIC\textsubscript{50}): –
  - Comment: 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
  - HGNC, UniProt: DNPEP, Q9ULA0
  - EC number: 3.4.11.21
  - Endogenous substrates: –
  - Selective inhibitors (pIC\textsubscript{50}): –
  - Inhibitors (pIC\textsubscript{50}): –
  - Comment: Hydrolyses CCK-8 (CCK, P06307) [297], angiotensin II (AGT, P01019) [307], neurokinin B (TAC3, Q9UHF0), chromogranin A (CHGA, P10645), kallidin (KNG1, P01042) [292]

- Leucyl-cysteinyl aminopeptidase
  - HGNC, UniProt: LNPEP, Q9UIQ6
  - EC number: 3.4.11.3
  - Selective inhibitors (pIC\textsubscript{50}): –
  - Inhibitors (pIC\textsubscript{50}): –
  - Comment: Hydrolyses AVP (AVP, P01178), oxytocin (OXT, P01178), kallidin (KNG1, P01042), [Met]enkephalin (PENK, P01210), dynorphin A (PDYN, P01213)

- Leukotriene A\textsubscript{4} hydrolase
  - HGNC, UniProt: LTA4H, P09960
  - EC number: 3.3.2.6
  - Selective inhibitors (pIC\textsubscript{50}): thiorphan
  - Inhibitors (pIC\textsubscript{50}): bestatin [300]
  - Comment: Hydrolyses CCK-8 (CCK, P06307) [297], angiotensin II (AGT, P01019) [290]

- Metalloproteinase (M) endopeptidase
  - HGNC, UniProt: MME, P08473
  - EC number: 3.4.24.11
  - Selective inhibitors (pIC\textsubscript{50}): captopril
  - Inhibitors (pIC\textsubscript{50}): 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].

- Angiotensin-converting enzyme
  - HGNC, UniProt: ACE, P12821
  - EC number: 3.4.15.1
  - Endogenous substrates: angiotensin I (AGT, P01019) > angiotensin II (AGT, P01019)
  - Selective inhibitors (pIC\textsubscript{50}): captopril
  - Comment: Hip-His Leu has been used experimentally as a probe for ACE1. ACE1 appears to express a distinct GPI hydrolase activity [296].

- Angiotensin-converting enzyme 2
  - HGNC, UniProt: ACE2, Q9BYF1
  - EC number: 3.4.15.1
  - Endogenous substrates: angiotensin I (AGT, P01019) > angiotensin-(1-9) (AGT, P01019) [290]
  - Selective inhibitors (pIC\textsubscript{50}): captopril
  - Comment: Abz-Ser-Pro-Tyr(NO\textsubscript{2})-OH has been used experimentally as a probe for ACE2

- Endothelin-converting enzyme 1
  - HGNC, UniProt: ECE1, P42892
  - EC number: 3.4.24.71
  - Endogenous substrates: ET-1 (EDN1, P05305), ET-2 (EDN2, P20800), ET-3 (EDN3, P14138)
  - Selective inhibitors (pIC\textsubscript{50}): SM19712 [305]
  - Comment: –

- Endothelin-converting enzyme 2
  - HGNC, UniProt: ECE2, O60344
  - EC number: 3.4.24.71
  - Endogenous substrates: ET-1 (EDN1, P05305), ET-2 (EDN2, P20800), ET-3 (EDN3, P14138)
  - Selective inhibitors (pIC\textsubscript{50}): –
  - Comment: –
| 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                                  | NPEPS5, P55786                    | –                                             | TRHDE, Q9UKU6               | XPNPEP1, Q9NQW7            | XPNPEP2, Q43895           |
| EC number                   | 3.4.11.18                                        | 3.4.11.14                         | 3.4.19.6                                      | 3.4.11.9                   | 3.4.11.18                  | 3.4.11.19                |

| 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, Q8IU7        | CPA1, P15085                  | CPA2, P48052                  | CP43, 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, Q9H42       | CPA5, Q8WXQ8      | CPA6, Q8N4T0      | CPB1, P15086                 | CPB2, Q96LY4                | 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                       | 3.4.17.-         | –                | 3.4.17.-                                  |
### Nomenclature

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

| Enzyme Name | HGNC, UniProt | EC number |
|-------------|---------------|-----------|
| N-Acetylated α-linked acidic dipeptidase-like 1 | NAALADL1, Q9UQQ1 | 3.4.17.21 |
| N-Acetylated α-linked acidic dipeptidase 2 | NAALAD2, Q9Y3Q0 | 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, stromelysins and matrilysins, as well as membrane type-MMP (MT-MMP).

| Enzyme Name | HGNC, UniProt | EC number 1 | EC number 2 |
|-------------|---------------|-------------|-------------|
| MMP1        | MMP1, P03956  | 3.4.24.7    | –           |
| MMP2        | MMP2, P08253  | 3.4.24.24   | –           |
| MMP3        | MMP3, P08254  | 3.4.24.17   | –           |
| MMP7        | MMP7, P09237  | 3.4.24.23   | –           |
| MMP8        | MMP8, P22894  | 3.4.24.34   | –           |
| MMP9        | MMP9, P14780  | 3.4.24.35   | –           |

| Enzyme Name | HGNC, UniProt | EC number 1 | EC number 2 |
|-------------|---------------|-------------|-------------|
| MMP10       | MMP10, P09238 | 3.4.24.22   | –           |
| MMP11       | MMP11, P24347 | 3.4.24.65   | –           |
| MMP12       | MMP12, P39900 | 3.4.24.23   | –           |
| MMP13       | MMP13, P45452 | 3.4.24.80   | –           |
| MMP14       | MMP14, P50281 | 3.4.24.80   | –           |
| MMP15       | MMP15, P51511 | 3.4.24.80   | –           |

| Enzyme Name | HGNC, UniProt | EC number 1 | EC number 2 |
|-------------|---------------|-------------|-------------|
| MMP16       | MMP16, P51512 | 3.4.24.-    | –           |
| MMP17       | MMP17, Q9ULZ9 | 3.4.24.-    | –           |
| MMP18       | MMP19, Q9542  | 3.4.24.-    | –           |
| MMP19       | MMP19, Q9542  | 3.4.24.-    | –           |
| MMP20       | MMP20, Q60882 | 3.4.24.-    | –           |
| MMP21       | MMP21, Q8N119 | 3.4.24.-    | –           |
| MMP22       | MMP22, Q75900 | 3.4.24.-    | –           |
| MMP23       | MMP23, Q9Y5R2 | 3.4.24.-    | –           |

### Footnotes

- S.P.H. Alexander et al. The Concise Guide to PHARMACOLOGY 2013/14: Enzymes. British Journal of Pharmacology (2013) 170, 1797–1867
- Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
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.

ADAMTS metallopeptidases

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

| Nomenclature | ADAMTS12 | ADAMTS13 |
|-------------|----------|----------|
| HGNC, UniProt | ADAMTS12, P58397 | ADAMTS13, Q76LX8 |
| Comment | Loss-of-function mutations of autoimmune antibodies are associated with thrombotic thrombocytopenic purpura |

### 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, Q9H4B0 | DPP4, P27487 | DPP7, Q9HUL4 |
| EC number | 3.4.16.5 | 3.4.16.2 | 3.4.16- | 3.4.16- | 3.4.14.5 | 3.4.14.2 |
| Endogenous substrates | Peptide | Peptide | glucagon-like peptide 1 |

### Further reading

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Protein serine/threonine kinases

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 β2-adrenoceptor agonists binding to the receptor lead to the consequent activation and dissociation of the heterotrimeric G protein Gs. Ga activates adenylyl cyclase activity, while Gβγ subunits perform other functions, one of which is to recruit βARK to phosphorylate serine/threonine residues in the cytoplasmic tail of the β2-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 Ca2+/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 N6-benzyl-cAMP (see Table) and 8-pCPT-2′-O-Me-cAMP, respectively [337].
Protein kinase A (PKA)

**Activators**
- N6 benzyl-cAMP

**Inhibitors (pIC50)**
- Rp-cAMPS

**Radioligands (Kd)**
- [3H]cAMP (Activator)

**Comments:** Other members of the PKA family are PRKX (X-linked protein kinase, PRKX, 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 PIP3, 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 (pIC50)**
- 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 Ca²⁺ 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**
- PKCa
- PKCb
- PKCc

**HGNC, UniProt**
- PRKCA, P17252
- PRKCB, P05771
- PRKCG, P05129

**Selective inhibitors (pIC50)**
- ruboxistaurin (8.3) [334], CGP53353 (6.4) [313]

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

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**Searchable database:** http://www.guidetopharmacology.org/index.jsp

**Full Contents of Concise Guide:** http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full

**Protein serine/threonine kinases**

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**S.P.H. Alexander et al. The Concise Guide to PHARMACOLOGY 2013/14: Enzymes. British Journal of Pharmacology (2013) 170, 1797-1867**
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.

Protein kinase G (PKG) 1 | Protein kinase G (PKG) 2
--- | ---
Nomenclature | PKG1 | PKG2
HGNC, UniProt | PRKG1, Q13976 | PRKG2, Q13237
EC number | 2.7.11.12 | 2.7.11.12
Selective inhibitors (pI50) | Rp-8-CPT-cGMPS [312] | –

Mitogen-activated protein kinases (MAP kinases)

Overview: MAP kinases (CMGC kinases, ENSF0000000137, 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.

mitogen-activated protein kinase 1 | mitogen-activated protein kinase 3
--- | ---
Nomenclature | MAPK1, P28482 | MAPK3, P27361
Common abbreviation | ERK2 | ERK1
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 | Common abbreviation | HGNC, UniProt | Selective inhibitors (pIC_{50}) |
|---------------|---------------------|---------------|---------------------------------|
| mitogen-activated protein kinase 8 | JNK1 | MAPK8, P45983 | SP600125 (7.4) [311] |
| mitogen-activated protein kinase 9 | JNK2 | MAPK9, P45984 | SP600125 (7.4) [311] |
| mitogen-activated protein kinase 10 | JNK3 | MAPK10, P53779 | 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 | Common abbreviation | HGNC, UniProt | Selective inhibitors (pIC_{50}) |
|---------------|---------------------|---------------|---------------------------------|
| mitogen-activated protein kinase 11 | p38β | MAPK11, Q15759 | SB202190 [341], SB203580 (pK 7.0) [324] |
| mitogen-activated protein kinase 12 | p38γ | MAPK12, P53778 | – |
| mitogen-activated protein kinase 13 | p38δ | MAPK13, O15264 | – |
| mitogen-activated protein kinase 14 | p38α | MAPK14, Q16539 | SB203580 (pK 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_{12/13} subunits [339].
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, Q90913        | 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) | CRIT               | CRIT, Q14578        | 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, Q60307       | 2.7.11.1  | See comment for MAST1                                                   |
| Microtubule associated serine/threonine kinase 4  | MAST4               | MAST4, Q15021       | 2.7.11.1  | See comment for MAST1                                                   |
| Microtubule associated serine/threonine kinase-like | MASTL               | MASTL, Q96GXS       | 2.7.11.1  | See comment for MAST1                                                   |
| large tumor suppressor kinase 1                   | LATS1               | LATS1, Q958SI       | 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, Q9NRMM       | 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                | PDK1, Q15208        | 2.7.11.1  | –                                                                        |
| protein kinase N1                                 | PKN1                | PKN1, Q15208        | 2.7.11.13 | PKN family members are activated by Rho, PIP3 and PDK1 [321]            |
| protein kinase N2                                 | PKN2                | PKN2, Q15208        | 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, Q7558S     | 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                | RPS6K4, Q75567      | 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 p70k, are activated by MAP kinase-mediated phosphorylation. | RSK protein kinases are also activated by phosphorylation by TORC1 and PDK1 [333]. Substrates include ribosomal S6 protein (RPS6, P62753), GS3β (P49841) [349] and the SHT2A receptor [348] |
| ribosomal protein S6 kinase, 70kDa, polypeptide 2 | p70S6Kβ              | RPS6KB2, Q9UB50     | 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 p90k 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 SHT2A receptor [348] |
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                    | MYLK, Q15746                | CalMII                        |
| HGNC, UniProt                                                                | –          | –               |                           | MYLK2, Q9H13                |                               |
| EC number                                                                    | 2.7.11.1   | 2.7.11.1        |                           | 2.7.11.18                  | 2.7.11.17                     |
| Endogenous activators                                                        | AMP        | –               | calmodulin (CALM2, CALM3, | calmodulin (CALM2, CALM3, CALM1, P62158) | calmodulin (CALM2, CALM3, CALM1, P62158) |
| Selective activators                                                         | AICA-riboside [318] | – | – | – | – |
| Selective inhibitors (pIC50)                                                  | 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 (ENSM00000001201, [350]), an upstream activator of calmodulin-dependent kinase.
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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<sub>1-5</sub>) 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.

| Nomenclature                      | Common abbreviation  | HGNC, UniProt      | EC number                                                                 | Comment                                                                 |
|-----------------------------------|----------------------|--------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| sphingosine kinase 1              | SPHK1                | SPHK1, Q9NYA1      | 2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP, sphinganine + ATP = sphinganine 1-phosphate + ADP | Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [359] |
| sphingosine kinase inhibitor [356]|                      |                    |                                                                          |                                                                          |
| ABC294640 [357], ROMe [358]       |                      |                    |                                                                          |                                                                          |

Sphingosine 1-phosphate phosphatase

| Nomenclature                      | Common abbreviation  | HGNC, UniProt      | EC number                                                                 | Comment                                                                                                                                 |
|-----------------------------------|----------------------|--------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| sphingosine-1-phosphate phosphatase 1 | SGPP1               | SGPP1, Q8WX5      | 3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate   | 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 phosphatase 2 | SGPP2               |                    |                                                                          |                                                                                                                                          |

Sphingosine 1-phosphate lyase

| Nomenclature                      | HGNC, UniProt      | EC number                                                                 | Cofactors                           | Comment                                                                 |
|-----------------------------------|--------------------|--------------------------------------------------------------------------|-------------------------------------|--------------------------------------------------------------------------|
| sphingosine-1-phosphate lyase 1   | SGPL1, Q9S470      | 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 T3 and T4, 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).

Tissue deiodinases. These are 1 TM selenoproteins that remove an iodine from T4 (3,3',5,5'-tetraiodothyronine) to generate T3 (3,3',5-triiodothyronine, a more potent agonist at thyroid hormone receptors) or rT3 (rT3, 3,3',5'-triiodothyronine, a relatively inactive analogue). DIO1 is also able to deiodinate RT3 to form 3,3'-diiodothyronine (T2). Iodotyrosine deiodinase is a 1TM homodimeric enzyme.

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