THE CONCISE GUIDE TO PHARMACOLOGY 2013/14: OVERVIEW

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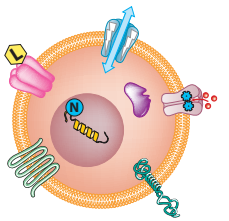

Abstract

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 from the IUPHAR database. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full.

This compilation of the major pharmacological targets is divided into seven areas of focus: G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear hormone receptors, transporters and enzymes. 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 & 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 GRAC and provides a permanent, citable, point-in-time record that will survive database updates.

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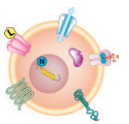
Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of Concise Guide: http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full



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An Introduction to the Concise Guide to PHARMACOLOGY 2013/14

The great proliferation of drug targets in recent years has driven the need to provide a logically-organised synopsis of the nomenclature and pharmacology of these targets. This is the underlying reason for this Guide to PHARMACOLOGY 2013/14, distributed with the British Journal of Pharmacology, and produced in association with NC-IUPHAR, the Nomenclature Committees of the International Union of Basic and Clinical Pharmacology. Our intent is to produce an authoritative but user-friendly publication, which allows a rapid overview of the key properties of a wide range of established or potential pharmacological targets. The aim is to provide information succinctly, so that a newcomer to a particular target group can identify the main elements 'at a glance'. It is not our goal to produce all-inclusive reviews of the targets presented; references to these are included in the Further Reading sections of the entries or, for many targets, the website www.guidetopharmacology.org provides access to more extensive information. The Guide to PHARMACOLOGY 2013/14 presents each entry, typically a circumscribed target class family on, wherever possible, a single page, so as to allow easy access and rapid oversight.

The list of targets present is, in many cases, a comprehensive reflection of the known targets within the particular group. Our philosophy has been to present data on human proteins wherever possible, both in terms of structural information and pharmacology. To this end, the HGNC gene nomenclature and UniProt unique ID are indicated to allow rapid access through free online databases for further information. In a few cases, where structural or pharmacological information is not available for human targets, we have used data from other species, as indicated. A priority in constructing these tables was to present agents which represent the most selective and which are available by donation or from commercial sources, now or in the near future.

The Guide is divided into seven further sections, which comprise pharmacological targets of similar structure/function. These are G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear hormone receptors, transporters and enzymes. In this overview are listed protein targets of pharmacological interest, which are not G protein-coupled receptors, ligand-gated ion channels, ion channels, nuclear hormone receptors, catalytic receptors, transporters or enzymes. In comparison with the Fifth Edition of the Guide to Receptors & Channels [1], we have added a number of new records, expanding the total to include over 2000 protein targets, primarily from increasing the content on transporters and enzymes.

The Editors of the Guide have compiled the individual records, taking advice from many Collaborators (listed on page 1452). Where appropriate, an indication is given of the status of the nomenclature, as proposed by NC-IUPHAR, published in Pharmacological Reviews. Where this guidance is lacking, advice from several prominent, independent experts has generally been obtained to produce an authoritative consensus, which attempts to fit in within the general guidelines from NC-IUPHAR [2]. Tabulated data provide ready comparison of selective agents and probes (radioligands and PET ligands, where available) within a family of targets and additional commentary highlights whether species differences or ligand metabolism are potential confounding factors. We recommend that any citations to information in the Concise Guide are presented in the following format:

Alexander SPH *et al.* (2013). The Concise Guide to PHARMACOLOGY 2013/14. *Br J Pharmacol* **170**: 1449–1867.

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Conflict of interest

The authors state that there are no conflicts of interest to disclose.

List of records presented

1454 Adiponectin receptors
1455 Fatty acid binding proteins
1457 Sigma receptors

Adiponectin receptors

Overview: Adiponectin receptors (provisional nomenclature, ENSFM00500000270960) respond to the 30 kDa complement-related protein hormone adiponectin (also known as *ADIPOQ*: adipocyte, C1q and collagen domain-containing protein; ACRP30, adipose most abundant gene transcript 1; apM-1; gelatin-binding protein: Q15848) originally cloned from adipocytes [4]. Although sequence data suggest 7TM domains, immunological evidence indicates that, contrary to typical 7TM topology, the carboxyl terminus is extracellular, while the amino terminus is intracellular [6]. Signalling through these receptors appears to avoid G proteins. Adiponectin receptors appear rather to stimulate protein phosphorylation via AMP-activated protein kinase and MAP kinase pathways [6], possibly through the protein partner *APPL1* (adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1, Q9UKG1 [5]). The adiponectin receptors are a class of proteins (along with membrane progestin receptors), which contain seven sequences of aliphatic amino acids reminiscent of GPCRs, but which are structurally and functionally distinct from that class of receptor.

Nomenclature	Adipo1 receptor	Adipo2 receptor
HGNC, UniProt	*ADIPOR1*, Q96A54	*ADIPOR2*, Q86V24
Rank order of potency	globular adiponectin > adiponectin	globular adiponectin = adiponectin

Comments: T-Cadherin (*CDH13*, P55290) has also been suggested to be a receptor for (hexameric) adiponectin [3].

Further reading

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Thundyil J, Pavlovski D, Sobey CG, Arumugam TV. (2012) Adiponectin receptor signalling in the brain. *Br J Pharmacol* **165**: 313–327. [PMID:21718299]

Fatty acid binding proteins

Overview: Fatty acid-binding proteins are low molecular weight (100–130 aa) chaperones for long chain fatty acids, fatty acyl CoA esters, eicosanoids, retinols, retinoic acids and related metabolites and are usually regarded as being responsible for allowing the otherwise hydrophobic ligands to be mobile in aqueous media. These binding proteins may perform functions extracellularly (*e.g.* in plasma) or transport these agents; to the nucleus to interact with nuclear receptors (principally PPARs and retinoic acid receptors [16]) or for interaction with metabolic enzymes. Although sequence homology is limited, crystallographic studies suggest conserved 3D structures across the group of binding proteins.

Preferred abbreviation	FABP1	FABP2	FABP3	FABP4	FABP5
Nomenclature	fatty acid binding protein 1, liver	fatty acid binding protein 2, intestinal	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)	fatty acid binding protein 4, adipocyte	fatty acid binding protein 5 (psoriasis-associated)
HGNC, UniProt	*FABP1*, P07148	*FABP2*, P12104	*FABP3*, P05413	*FABP4*, P15090	*FABP5*, Q01469
Rank order of potency	stearic acid, oleic acid > palmitic acid, linoleic acid > arachidonic acid, α-linolenic acid [13]	stearic acid > palmitic acid,oleic acid > linoleic acid > arachidonic acid, α-linolenic acid [13]	stearic acid, oleic acid, palmitic acid > linoleic acid, α-linolenic acid, arachidonic acid [13]	oleic acid, palmitic acid, stearic acid, linoleic acid > α-linolenic acid, arachidonic acid [13]	–
Comment	A broader substrate specificity than other FABPs, binding two fatty acids per protein [18]	Crystal structure of the rat FABP2 [15]	Crystal structure of the human FABP3 [19]	–	Crystal structure of the human FABP5 [11]

Preferred abbreviation	FABP6	FABP7	FABP8	FABP9	FABP12
Nomenclature	fatty acid binding protein 6, ileal	fatty acid binding protein 7, brain	peripheral myelin protein 2	fatty acid binding protein 9, testis	fatty acid binding protein 12
HGNC, UniProt	*FABP6*, P51161	*FABP7*, O15540	*PMP2*, P02689	*FABP9*, Q0Z7S8	*FABP12*, A6NFH5
Comment	Able to transport bile acids [20]	Crystal structure of the human FABP7 [7]	*In silico* modelling suggests that FABP8 can bind both fatty acids and cholesterol [12]	–	–

Preferred abbreviation	RBP1	RBP2	RBP3	RBP4	RBP5
Nomenclature	retinol binding protein 1, cellular	retinol binding protein 2, cellular	retinol binding protein 3, interstitial	retinol binding protein 4, plasma	retinol binding protein 5, cellular
HGNC, UniProt	*RBP1*, P09455	*RBP2*, P50120	*RBP3*, P10745	*RBP4*, P02753	*RBP5*, P82980
Rank order of potency	–	stearic acid > palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid [14]	–	–	–

Preferred abbreviation	RBP7	RLBP1	CRABP1	CRABP2
Nomenclature	retinol binding protein 7, cellular	retinaldehyde binding protein 1	cellular retinoic acid binding protein 1	cellular retinoic acid binding protein 2
HGNC, UniProt	*RBP7*, Q96R05	*RLBP1*, P12271	*CRABP1*, P29762	*CRABP2*, P29373
Rank order of potency	–	11-*cis*-retinal, 11-*cis*-retinol > 9-*cis*-retinal, 13-*cis*-retinal, 13-*cis*-retinol, all-*trans*-retinal, retinol [8]	all-trans-retinoic acid > 9-cis-retinoic acid stearic acid > palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid [14]	–

Comments: Although not tested at all FABPs, BMS309403 exhibits high affinity for FABP4 (pIC_{50} ~8.8) compared to FABP3 or FABP5 (pIC_{50} <6.6, [9,17]). HTS01037 is reported to interfere with FABP4 action [10]. Multiple pseudogenes for the FABPs have been identified in the human genome.

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Sigma receptors

Overview: Although termed 'receptors', the evidence for coupling through conventional signalling pathways is lacking. Initially described as a subtype of opioid receptors, there is only a modest pharmacological overlap and no structural convergence with the G protein-coupled receptors. A wide range of compounds, ranging from psychoactive agents to antihistamines, have been observed to bind to these sites, which appear to be intracellular.

Nomenclature	σ1 (sigma non-opioid intracellular receptor 1)	σ2
HGNC, UniProt	*SIGMAR1*, Q99720	–
Selective agonists	(+)-SK&F10047, (RS)-PPCC (pK_i 8.8) [25], PRE-084 (pIC_{50} 7.4) [26]	PB-28 (pK_i 8.3) [21]
Selective antagonists	NE-100 (pIC_{50} 8.4) [24], BD-1047 (pIC_{50} 7.4) [23]	(RS)-SM21 (pIC_{50} 7.2) [22]
Radioligands (K_d)	[^{3}H]-pentazocine (Agonist)	[^{3}H]-di-o-tolylguanidine (Agonist)

Comments: (-)-pentazocine also shows activity at opioid receptors. There is no molecular correlate of the sigma2 receptor.

Further reading

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