Overview


Abstract

The Concise Guide to PHARMACOLOGY 2017/18 is the third in this series of biennial publications. This version provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), 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.

In addition to this overview, in which are identified 'Other protein targets' which fall outside of the subsequent categorisation, there are eight areas of focus: G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, other ion channels, nuclear hormone receptors, catalytic receptors, enzymes and transporters. These are presented in a landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2017, and supersedes data presented in the 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature Committee of the Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

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S47 Bradykinin receptors
S48 Calcitonin receptors
S50 Calcium-sensing receptor

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

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Introduction


This current edition, the Concise Guide to PHARMACOLOGY 2017/18, is the latest snapshot of the database in print form, following on from the Concise Guide to PHARMACOLOGY 2015/16. Its development was again led by the British Pharmacological Society (BPS) and the International Union of Basic and Clinical Pharmacology (IUPHAR), with financial support from the Wellcome Trust (099156/Z/12/Z) and the University of Edinburgh. We are extremely grateful to the British Pharmacological Society and the International Union of Basic and Clinical Pharmacology for their support. Data from NC-IUPHAR subcommittees and beyond, who have assisted in the construction of the Concise Guide 2017/18 and the online database www.GuideToPHARMACOLOGY.org, have also contributed towards this edition.

full contents of ConciseGuide:
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The support team here are no outl of interest to disclose.

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Adiponectin receptors

Overview: Adiponectin receptors respond most abundantly to native adiponectin. Modelled based on the crystal structure, these receptors appear to belong to a protein family with a novel domain-containing structure. Despite the adiponectin receptors' putative extracellular site, the carboxyl terminus is extracellular, while the amino terminus is intracellular. Although not structurally related, the adiponectin receptors signal through a novel domain containing ceramidase activity.

Nomenclature

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<th>Adipo2 receptor</th>
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<td>ADIPOR2, Q86V24</td>
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</table>

Rank order of potency

1. adipo1 receptor
2. adipo2 receptor
3. globular adiponectin
4. adiponectin

Comments

Adiponectin receptor (CD36, Q42972) has been assigned to be a receptor for (human adiponectin [36].


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

Further reading on Blood coagulation components


Searchable database: http://www.guidetopharmacology.org

Further reading on Blood coagulation components

Blood coagulation components

Nomenclature
coagulation factor V
coagulation factor VIII
serpin family C member 1
HGNC, UniProt F5, P12259
F8, P00451
SERPINC1, P01008

Selective activators
- heparin (pKd 7.8) [26], fondaparinux (pKd 7.5) [62], dalteparin [32], danaparoid [16, 56], enoxaparin [19], tinzaparin [20]

Selective inhibitors
drotrecogin alfa [36, 37] –

Other protein targets
Blood coagulation components
Non-enzymatic BRD containing proteins

Overview

Bromodomain-containing proteins interact with acetylated lysine residues, such as histones, to regulate gene transcription. List of proteins are complexes of bromodomain-containing proteins for which sufficient pharmacology exists.

Nomenclature

- transthyretin (TTR)
- transthyretin (TTR)

Further reading on the development of non-BET bromodomain chemical probes.

http://www.guidetopharmacology.org/index.jsp


SEARCHABLE DATABASE: http://www.guidetopharmacology.org/index.jsp

Non-enzymatic BRD containing proteins

Carrier proteins

Other protein targets

→ Bromodomain-containing proteins

Overview

Transferrin (TFR) is a homotetrameric protein that plays a key role in the transport of iron in the body. It binds to the transferrin receptor (TFR) on the surface of cells, where it is internalized and released into the cell cytoplasm. The released iron is then used for cellular processes such as heme biosynthesis and DNA repair.

Nomenclature

- transferrin (TFR)
- transferrin (TFR)

Further reading on transferrin:

http://www.guidetopharmacology.org/index.jsp


SEARCHABLE DATABASE: http://www.guidetopharmacology.org/index.jsp

Non-enzymatic BRD containing proteins

Carrier proteins

Other protein targets

→ Bromodomain-containing proteins
**Overview**

CD molecules

Other protein targets

→ CD molecules

Overview: Cluster of differentiation refers to a group of cell-surface proteins that are encoded by genes that are clustered on the same chromosome. Many members of the group have identical Nomenclature and are targeted for therapeutic gain using antibodies.

Nomenclature

- CD2
- CD3
- CD20 (membrane-spanning 4-domains, subfamily A, member 1)
- CD33
- CD52

HGNC, UniProt

- CD2, P06729
- CD3E, P07766
- MS4A1, P11836
- CD33, P20138
- CD52, P31358

Common abbreviations

- SIGLEC-3
- Alefacept
- Catumaxomab
- Muromonab-CD3
- Ofatumumab
- Rituximab
- Ibritumomab tiuxetan
- Obinutuzumab
- Tositumomab
- Lintuzumab
- Gemtuzumab ozogamicin
- Alemtuzumab

**Antibodies**

- Binding

- Alefacept (Inhibition)
- Catumaxomab (Inhibition)
- Muromonab-CD3 (Inhibition)
- Ofatumumab (Inhibition)
- Rituximab (Inhibition)
- Ibritumomab tiuxetan (Inhibition)
- Obinutuzumab (Inhibition)
- Tositumomab (Inhibition)
- Lintuzumab (Inhibition)
- Gemtuzumab ozogamicin (Inhibition)
- Alemtuzumab (Inhibition)

**CD molecules S9**

Full Contents of Concise Guide: http://www.guidetopharmacology.org/index.jsp

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

CD molecules
Nomenclature

- **CD80**
  - HGNC, UniProt: CD80, P33681

- **CD86**
  - HGNC, UniProt: CD86, P42081

- **CTLA4**
  - HGNC, UniProt: CTLA4, P16410

- **PDCD1**
  - HGNC, UniProt: PDCD1, Q15116

- **CD300A**
  - HGNC, UniProt: CD300A, Q9UGN4

**Common abbreviations**

- **CTLA-4**
- **PD-1**

**Antibodies**

- **Ipilimumab** ($pK_d > 9$) [28]
- **Tremelimumab** ($pK_d 8.9$) [30]
- **Pembrolizumab** ($pK_d \sim 10$) [11]
- **Nivolumab** ($pK_d 9.1$) [28, 38, 40]

**Comment:** The endogenous ligand for human PD-1 is programmed cell death 1 ligand 1 (PD-L1; aka CD274, Q9NZQ7) and programmed cell death 1 ligand 2 (PD-L2; PDCD1LG2).

These ligands are cell surface peptides, normally involved in immune system regulation. Expression of PD-1 by cancer cells induces immune tolerance and evasion of immune system attack. Anti-PD-1 monoclonal antibodies are used to induce immune checkpoint blockade as a therapeutic intervention in cancer, effectively re-establishing immune vigilance. Pembrolizumab was the first anti-PD-1 antibody to be approved by the US FDA.

**Further reading on CD molecules**


**Searchable database:**

http://www.guidetopharmacology.org/index.jsp

**Further reading on Methyllysine reader proteins**

Fatty acid-binding proteins

Overview:

Fatty acid-binding proteins (FABPs) are a group of low molecular weight (100-130 aa) chaperones for long chain fatty acids, fatty acyl CoA esters, eicosanoids, retinols, retinoic acids and related metabolites. They 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 [70]) or for interaction with metabolic enzymes. Although sequence homology is limited, crystallographic studies suggest conserved 3D structures across the group of binding proteins.

### Nomenclature

- **Fatty acid binding protein 1**: FABP1, HGNC, UniProt P07148
- **Fatty acid binding protein 2**: FABP2, HGNC, UniProt P12104
- **Fatty acid binding protein 3**: FABP3, HGNC, UniProt P05413
- **Fatty acid binding protein 4**: FABP4, HGNC, UniProt P15090
- **Fatty acid binding protein 5**: FABP5, HGNC, UniProt Q01469
- **Fatty acid binding protein 6**: FABP6, HGNC, UniProt P51161
- **Fatty acid binding protein 7**: FABP7, HGNC, UniProt O15540
- **Peripheral myelin protein 2**: FABP9, HGNC, UniProt Q0Z7S8
- **Fatty acid binding protein 12**: FABP12, HGNC, UniProt A6NFH5

### Rank order of potency

- Stearic acid
- Oleic acid
- Palmitic acid
- Linoleic acid
- Arachidonic acid
- α-Linolenic acid

### Inhibitors

- Fenofibrate (pKi 7.6) [12] – Rat
- Fenofibric acid (pKi 6.5) [12] – Rat
- HTS01037 (pKi 5.1) [30] – Mouse

### Comments

- A broader substrate specificity than other FABPs, binding two fatty acids per protein [82].
- Crystal structure of the rat FABP2 [69].
- Crystal structure of the human FABP3 [91].
- A broader substrate specificity than other FABPs, binding two fatty acids per protein [82].
- Crystal structure of the human FABP5 [31].
- Able to transport bile acids [95].
- Crystal structure of the human FABP7 [5].
- In silico modelling suggests that FABP8 can bind both fatty acids and cholesterol [50].

### Searchable database

http://www.guidetopharmacology.org/index.jsp

Nomenclature

**retinol binding protein 1**
HGNC, UniProt: RBP1, P09455

**retinol binding protein 2**
HGNC, UniProt: RBP2, P50120

**retinol binding protein 3**
HGNC, UniProt: RBP3, P10745

**retinol binding protein 4**
HGNC, UniProt: RBP4, P02753

**retinol binding protein 5**
HGNC, UniProt: RBP5, P82980

**retinol binding protein 7**
HGNC, UniProt: RBP7, Q96R05

Rank order of potency
- stearic acid > palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid

Inhibitors
- A1120 (pIC₅₀ 7.8)

Comments:
Although not tested at all FABPs, BMS309403 exhibits high affinity for FABP4 (pIC₅₀ 8.8) compared to FABP3 or FABP5 (pIC₅₀ < 6.6).

HTS01037 is reported to interfere with FABP4 action.

Ibuprofen displays some selectivity for FABP4 (pIC₅₀ 5.5) relative to FABP3 (pIC₅₀ 3.5) and FABP5 (pIC₅₀ 3.8).

Fenofibric acid displays some selectivity for FABP5 (pIC₅₀ 5.5) relative to FABP3 (pIC₅₀ 4.5) and FABP4 (pIC₅₀ 4.6).

Multiple pseudogenes for the FABPs have been identified in the human genome.

Further reading on Fatty acid-binding proteins

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

Full Contents of Concise Guide:
The canonical Notch signalling pathway has four type I transmembrane Notch receptors (Notch1-4) and five ligands (DLL1, 2 and 3, and Jagged 1-2). Each member of this highly conserved receptor family plays a unique role in cell-fate determination during embryogenesis, differentiation, tissue patterning, proliferation and cell death [2]. As the Notch ligands are also membrane bound, cells have to be in close proximity for receptor-ligand interactions to occur. Cleavage of the intracellular domain (ICD) of activated Notch receptors by γ-secretase is required for downstream signalling and Notch-induced transcriptional modulation [18, 57, 71, 89]. This is why γ-secretase inhibitors can be used to downregulate Notch signalling and explains their anti-cancer action. One such small molecule is RO4929097 [47], although development of this compound has been terminated following an unsuccessful Phase II single agent clinical trial in metastatic colorectal cancer [78].

Aberrant Notch signalling is implicated in a number of human cancers [41, 59, 74, 85]. Pharmaceutical inhibitors of Notch signalling such as demcizumab and tarextumab are being actively investigated as novel anti-cancer agents [64].

### Nomenclature

<table>
<thead>
<tr>
<th>Notch</th>
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<td>NOTCH4</td>
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### Comments

- Notch 4 is a potential therapeutic molecular target for triple-negative breast cancer [42, 55].

### Further reading on Notch receptors

### 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; the crystal structure of the sigma1 receptor suggests a trimeric structure consisting of a single monomeric subunit, with the bulk of the protein facing the cytosol. A wide range of compounds, ranging from psychoactive agents to antihistamines, have been observed to bind to these sites.

#### Nomenclature

- **sigma non-opioid intracellular receptor 1** (σ2)
- **HGNC, UniProt**
- **SIGMAR1**, Q99720

#### Selective agonists

- PRE-084
- (+)-SKF 10.047

#### Selective antagonists

- NE-100 (pIC₅₀ 8.4)
- BD-1047 (pIC₅₀ 7.4)

#### Labelled ligands

- [³H]pentazocine (Agonist)
- [³H]-di-o-tolylguanidine (Agonist)

#### Comments

- (-)-pentazocine also shows activity at opioid receptors. The sigma2 receptor has recently been reported to be TMEM97 [Q5BJF2], part of the NPC1 complex, the Niemann-Pick C1 protein, a 13-TM cholesterol-binding protein.

#### Further reading on Sigma receptors


#### Searchable database

- http://www.guidetopharmacology.org/index.jsp

#### Full Contents of Concise Guide

Tubulins

Tubulins are a family of integral proteins most commonly associated with microtubules, part of the cytoskeleton. They are exploited for their potential in cancer chemotherapy as targets for agents derived from natural products; taxanes, colchicine and vinca alkaloids. These are thought to act primarily through β-tubulin, thereby interfering with the normal processes of tubulin polymer formation and disassembly.

Nomenclature

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Inhibitors

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<td>vinblastine</td>
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<td>eribulin</td>
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<td>combretastatin</td>
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Further reading on Tubulins

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<td>Gadadhar S et al</td>
<td>2017</td>
<td>The tubulin code at a glance</td>
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Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
