THE CONCISE GUIDE TO PHARMACOLOGY 2017/18

Citation for published version:

Digital Object Identifier (DOI):
10.1111/bph.13880

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published in:
British Journal of Pharmacology

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Nuclear hormone receptors

Overview

Nuclear hormone receptors are specialised transcription factors that bind to DNA elements and regulate gene transcription. They are classified into two major subclasses: steroid hormone receptors and other nuclear receptors. Steroid hormone receptors are typically dimeric entities and are thought to be resident outside the nucleus in the unliganded state in a complex with chaperone proteins, which are liberated upon agonist binding. Migration to the nucleus and interaction with other regulators of gene transcription, leading to changes in gene transcription, include RNA polymerase, acetyltransferases and deacetylases, allows gene transcription to be regulated. Non-selective pharmacology (where available), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Steroid hormone receptors function typically as homo- or heterodimers to specific consensus sequences of DNA (response elements) in the promoter region of particular target genes. They regulate (either promoting or repressing) transcription upon agonist binding. Selectivity of gene regulation is brought about through interaction of nuclear receptors with particular consensus sequences of DNA, which are arranged typically as repeats or inverted palindromes to allow accumulation of multiple transcription factors in the promoter region of genes. They typically exhibit a greater distribution of binding sites compared to other nuclear hormone receptors, generating a large multiprotein complex.

Endogenous agonists are hydrophobic entities which, when bound to the receptor promote conformational changes to the receptor to allow recruitment (or dissociation) of protein partners, which may have regulatory functions. Transcriptional activity of the receptor is then modulated by the activity of these partners, which may include additional transcription factors. Transcriptional activity of the receptor is further modified by the activity of co-activators and co-repressors, which may include additional transcription factors. Many nuclear hormone receptors also contain a transcriptional repression domain, which may be involved in the repression of transcription upon agonist binding.

Nuclear hormone receptors are a diverse group of proteins that are involved in the regulation of gene expression. They are involved in the regulation of a wide range of biological processes, including development, metabolism, reproduction, and immunity. They are also involved in the regulation of many diseases, including cancer and metabolic disorders. The study of nuclear hormone receptors is therefore important for understanding the regulation of gene expression and for developing new therapeutic strategies.
1A. Thyroid hormone receptors

**Overview**

The thyroid hormone receptor (TR) family includes the thyroid hormone receptors (TRα, TRβ) and the retinoic acid receptors (RAREs). These receptors play a crucial role in the regulation of thyroid hormone levels and cellular responses.

**Nomenclature**

- **TRα** and **TRβ**
- **Sobetirome**

**Rank order of potency**

- Triiodothyronine > Triiodothyronine > Thyroxine

**Agonists**

- **Dextrothyroxine**

**Comments**

- **Non-genomic actions**
- **Interactions with integrin αVβ3**

**Further reading**

- Davis PJ et al. (2016) Non-genomic actions of thyroid hormone. Nat Rev Endocrinol 12:111-21
- Elbers LP et al. (2016) Thyroid hormone mimetics: the past, current status and future challenges.

**Searchable database**

[http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
IC. Peroxisome proliferator-activated receptors

Overview

Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear hormone receptors that are activated by the vitamin A-derived agonists, such as retinoic acid (RA), all-trans-retinoic acid (ATRA), and the immune response. PPARs have many potential endogenous ligands, including fatty acids and their oxidation products, as well as many non-steroidal anti-inflammatory drugs, such as indomethacin and sulindac. These receptors are activated by ligands and form a heterodimer with members of the retinoid X receptor family. PPARs have many potential endogenous ligands, including fatty acids and their oxidation products, as well as many non-steroidal anti-inflammatory drugs, such as indomethacin and sulindac. These receptors are activated by ligands and form a heterodimer with members of the retinoid X receptor family.

Comments

Further reading on IC. Peroxisome proliferator-activated receptors

Nuclear hormone receptors

1C. Peroxisome proliferator-activated receptors

Overview

Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear hormone receptors that are activated by the vitamin A-derived agonists, such as retinoic acid (RA), all-trans-retinoic acid (ATRA), and the immune response. PPARs have many potential endogenous ligands, including fatty acids and their oxidation products, as well as many non-steroidal anti-inflammatory drugs, such as indomethacin and sulindac. These receptors are activated by ligands and form a heterodimer with members of the retinoid X receptor family. PPARs have many potential endogenous ligands, including fatty acids and their oxidation products, as well as many non-steroidal anti-inflammatory drugs, such as indomethacin and sulindac. These receptors are activated by ligands and form a heterodimer with members of the retinoid X receptor family.

Comments

Further reading on IC. Peroxisome proliferator-activated receptors

Nuclear hormone receptors

1B. Retinoic acid receptors

Overview

Retinoic acid receptors are a family of nuclear hormone receptors that are activated by the vitamin A-derived agonists, such as retinoic acid (RA), all-trans-retinoic acid (ATRA), and the immune response. Retinoic acid receptors have many potential endogenous ligands, including fatty acids and their oxidation products, as well as many non-steroidal anti-inflammatory drugs, such as indomethacin and sulindac. These receptors are activated by ligands and form a heterodimer with members of the retinoid X receptor family. Retinoic acid receptors have many potential endogenous ligands, including fatty acids and their oxidation products, as well as many non-steroidal anti-inflammatory drugs, such as indomethacin and sulindac. These receptors are activated by ligands and form a heterodimer with members of the retinoid X receptor family.

Comments

Further reading on 1B. Retinoic acid receptors
Nuclear hormone receptors

Peroxisome proliferator-activated receptor-α
Peroxisome proliferator-activated receptor-β/δ
Peroxisome proliferator-activated receptor-γ

Nomenclature

Peroxisome proliferator-activated receptor-α (PPARA)
Peroxisome proliferator-activated receptor-β/δ (PPARD)
Peroxisome proliferator-activated receptor-γ (PPARG)

Selective agonists

GW7647
CP-775146
pirinixic acid
gemfibrozil
GW0742X
GW501516
bardoxolone
rosiglitazone
troglitazone
pioglitazone
ciglitazone

Selective antagonists

GW6471
GSK0660
T0070907
GW9662
CDDO-Me

Comments: As with the estrogen receptor antagonists, many agents show tissue-selective efficacy (e.g. [12, 109, 124]). Agonists with mixed activity at PPARα and PPARγ have also been described (e.g. [35, 52, 159]).

Further reading on 1C. Peroxisome proliferator-activated receptors


1D. Rev-Erb receptors

Nuclear hormone receptors

Rev-Erb receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]) have yet to be officially paired with an endogenous ligand, but are thought to be activated by heme.

Nomenclature

Rev-Erb-α (NR1D1)
Rev-Erb-β (NR1D2)

Endogenous agonists

heme

Selective agonists

GSK4112

Selective antagonists

SR8278 (pIC_{50} 6.5)
1F. Retinoic acid-related orphans

Overview: Retinoid X receptor-related orphan receptors (ROR, nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]) have yet to be assigned a definitive endogenous ligand. Although RORs may be agonized with a variety of synthetic and cholesterol [66], tretinoin shows selectivity for RORβ within the ROR family [136]. RORα has been suggested to be a nuclear receptor responding to melatonin [154].

<table>
<thead>
<tr>
<th>Endogenous Agonist</th>
<th>Selective Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol [66], [114]</td>
<td>7-Hydroxycholesterol [14], Cholesterol sulphate [14, 66], Cholesterol [66], [114]</td>
</tr>
</tbody>
</table>

Comments: Nuclear hormone receptors

Further reading on 1F. Retinoic acid-related orphans


1H. Liver X receptor-like receptors

Overview: Liver X and farnesoid X receptors (LXR and FXR, nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [105]) are members of the fasteroid analogue-activated nuclear receptor subfamily, which form heterodimers with members of the retinoid X receptor family. Endogenous ligands for LXR include hydroxycholesterols (OHC), while FXR appear to be activated by bile acids.

Nuclear hormone receptors

Systematic nomenclature

<table>
<thead>
<tr>
<th>Systematic name</th>
<th>Accession</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR1H4</td>
<td>Q96RI1</td>
</tr>
<tr>
<td>NR1H4P</td>
<td>–</td>
</tr>
<tr>
<td>NR1H3</td>
<td>Q13133</td>
</tr>
<tr>
<td>NR1H2</td>
<td>P55055</td>
</tr>
</tbody>
</table>

Potency order

- Cholesterol > lithocholic acid, deoxycholic acid, - 20S-hydroxycholesterol, 24(S)-hydroxycholesterol > 25-hydroxycholesterol, 27-hydroxycholesterol [79]
- 20S-hydroxycholesterol, 22R-hydroxycholesterol, 24(S)-hydroxycholesterol > 25-hydroxycholesterol, 27-hydroxycholesterol [79]

Endogenous agonists

- Lanosterol [113]

Selective agonists

- GW4064 [94], obeticholic acid [116], fexaramine [36]

Selective antagonists

- Guggulsterone (pIC50 5.7–6) [157]

1I. Vitamin D receptor-like receptors

Overview: Vitamin D (VDR), Pregnane X (PXR) and Constitutive Androstane (CAR) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]). While VDR has been long recognized as the endogenous ligand for the VDR receptor, the function of PXR and CAR remains ambiguous [163]. HNF4α has been identified as the endogenous ligand for CAR, although the function of CAR remains uncertain [6].

Nomenclature

- Vitamin D receptor (VDR)
- Pregnane X receptor (PXR)
- Constitutive Androstane receptor (CAR)

Endogenous agonists

- 1,25-dihydroxyvitamin D3 [11, 39]
- 17β-estradiol [64]

Selective agonists

- PBMC
- DOCA
- TCPOBOP [141–150]
- CITCO [91–96]
- lovastatin [81–86]
- rifampicin [15–16]
- seocalcitol [28–153]
- doxercalciferol [52, 152–153]
- 5β-pregnane-3,20-dione [64–153]
- littoralin [15]
- MRC-9647 [18–140]
- ZK159222 [42, 60–61]
- TCPOBOP [141–150]
- CITCO [91–96]

Selective antagonists

- TEI-9647 (pIC50 8.2) [126–150]
- ZK159222 (pIC50 7.5) [42, 60–61]
- clotrimazole [107–150]
- T0901317 [68–71]

Further reading on 1I. Vitamin D receptor-like receptors


2A. Hepatocyte nuclear factor-4 receptors

Overview: The nomenclature of hepatocyte nuclear factor-4 receptors is agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6].

Nomenclature

- HNF4α
- HNF4β
- HNF4γ

Endogenous agonists

- Linoleic acid [163–170]

Controls

- HNF4α
- HNF4β
- HNF4γ

Further reading on 2A. Hepatocyte nuclear factor-4 receptors

- Unpublished data

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


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


### 2B. Retinoid X receptors

**Overview:** Retinoid X receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors) are NR2B family members activated by alitretinoin and the RXR-selective agonists bexarotene and LG100268, sometimes referred to as exinoids. The RXR-selective agonists UVI3003 and HX531 have been described as pan-RXR antagonists. These receptors form RXR-RXR heterodimers and RXR-RXR homodimers.

**Nomenclature**

- Retinoid X receptor-α (systematic nomenclature NR2B1, HGNC, UniProt RXRA, P19793)
- Retinoid X receptor-β (systematic nomenclature NR2B2, HGNC, UniProt RXRB, P28702)
- Retinoid X receptor-γ (systematic nomenclature NR2B3, HGNC, UniProt RXRG, P48443)

**Sub/family-selective agonists**

- Bexarotene
  - **Selective agonists** CD3254
  - **Sub/family-selective agonists**
  - **Selective antagonists**

**Endogenous agonists**

- Linoleic acid

**Selective antagonists**

- BI6015

**Comments**

- HNF4α has constitutive transactivation activity (163)

**Further reading on 2A. Hepatocyte nuclear factor-4 receptors**


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**Searchable database:**

[http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Further reading on 2C. Testicular receptors


Nomenclature

TLX

PNR

Systematic nomenclature NR2E1 NR2E3

HGNC, UniProt

NR2E1, Q9Y466

NR2E3, Q9Y5X4

Comments

Gene disruption is associated with abnormal brain development [75, 104].

Further reading on 2E. Tailless-like receptors


2F. COUP-TF-like receptors

Overview:

COUP-TF-like receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]) have yet to be officially paired with endogenous ligands. COUP-TF-like receptors (nomenclature) are agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors on 2E. Tailless-like receptors.

Nuclear hormone receptors → 2F. COUP-TF-like receptors

Further reading on 2E. Tailless-like receptors

Searchable database:

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

Full Contents of Concise Guide:

3B. Estrogen-related receptors

Overview: Estrogen-related receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]) have yet to be officially paired with an endogenous ligand. These are called orphan receptors.

Nomenclature

Estrogen-related receptor-α (ESRRA)

Systematic nomenclature NR3B1

HGNC, UniProt: ESRRA, P11474

Comments: Activated by some dietary flavonoids [138]; activated by the synthetic agonist GSK4716 [181] and blocked by XCT790 [156]. May be activated by DY131 [162].

- Further reading on 3B. Estrogen-related receptors


Divekar SD et al. (2016) Estrogen-related receptor β (ERRβ)-reassurance of re-assurance? Nucl Recept Signal 14:e002 [PMID:27507929]


### 5A. Fushi tarazu F1-like receptors

**Overview:** Fushi tarazu F1-like receptors (nominal nomenclature) are accepted by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6](http://www.guidetopharmacology.org/index.jsp) and are identified in the database of the British Pharmacological Society.

<table>
<thead>
<tr>
<th>5A. Fushi tarazu F1-like receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name</strong></td>
</tr>
<tr>
<td>NR5A1</td>
</tr>
<tr>
<td>NR5A2</td>
</tr>
</tbody>
</table>

#### Further reading on 5A. Fushi tarazu F1-like receptors


Garattini E et al. (2016) Lipid sensors, enigmatic orphan and orphan nuclear receptors as therapeutic targets in breast-cancer. Oncotarget. 7:42661-42682 [PMID:26894976]


Further reading on 4A. Nerve growth factor IB-like receptors


6A. Germ cell nuclear factor receptors

Overview: Germ cell nuclear factor receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]) have yet to be clearly paired with an endogenous ligand.

Nomenclature

**Germ cell nuclear factor**

- **Systematic nomenclature**: NR6A1
- **HGNC**: NR6A1, Q15406

Further reading on 6A. Germ cell nuclear factor receptors


0B. DAX-like receptors

Overview: DAX-like receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [6]) have yet to be clearly paired with an endogenous ligand.

Nomenclature

**DAX1**

- **Systematic nomenclature**: NR0B1, NR0B2
- **HGNC**: NR0B1, P51843, NR0B2, Q15466

Further reading on 0B. DAX-like receptors

3A. Estrogen receptors

Steroid hormone receptors
→ Nuclear hormone receptors

### Overview

Estrogen receptors (ER) regulate diverse physiological processes involved in the regulation of target genes and the magnitude of the response, be it via functional monomers that can dimerize to form functional or non-functional receptors. For example, alternative splicing of PR mRNA produces A and B monomers that combine to produce non-functional receptors. Functional AA, AB and BB receptors with distinct characteristics can dimerize to form functional receptors that can bind to target DNA, interact with DNA and coregulators to form functional transcription complexes. Together, these nuclear hormone receptors regulate diverse physiological processes through the regulation of target genes and the magnitude of the response.

### Functional Monomers

Functional monomers that can bind to target DNA, interact with DNA and coregulators to form functional transcription complexes.

### Non-Functional Monomers

Non-functional monomers that can bind to target DNA, interact with DNA and coregulators to form non-functional transcription complexes.

### Alternative Splicing

Alternative splicing of PR mRNA produces A and B monomers that combine to produce non-functional receptors. For example, alternative splicing of PR mRNA produces A and B monomers that combine to produce non-functional receptors. Functional AA, AB and BB receptors with distinct characteristics can dimerize to form functional receptors that can bind to target DNA, interact with DNA and coregulators to form functional transcription complexes. Together, these nuclear hormone receptors regulate diverse physiological processes through the regulation of target genes and the magnitude of the response.

### Nomenclature

Nomenclature includes systematic and functional nomenclature. Systematic nomenclature includes NR3A1, NR3A2, and NR3A3, while functional nomenclature includes A, B, and BB receptors.

### Post-Translational Modifications

Post-translational modifications of ER include phosphorylation, acetylation, and ubiquitination, which affect the biological response of ER.

### Intracellular Localization

Intracellular localization of ER includes nuclear localization and cytoplasmic localization.

### Ligand Binding

Ligand binding to ER leads to conformational changes, which affect the biological response of ER.

### Genetic Polymorphisms

Genetic polymorphisms of ER affect the biological response of ER and are involved in disease susceptibility.

### Alternative Splicing

Alternative splicing of ER affects the biological response of ER and is involved in disease susceptibility.

### Endogenous Agonists

Endogenous agonists of ER include estradiol, estrone, and estriol.

### Endogenous Antagonists

Endogenous antagonists of ER include progesterone and dihydrotestosterone.

### Pharmacological Actions

Pharmacological actions of ER include transcriptional modulation of target genes, cell cycle regulation, and regulation of cellular differentiation.

### Clinical Relevance

Clinical relevance of ER includes role in breast cancer, hormone replacement therapy, and endometriosis.

### Further Reading

Further reading on ER includes therapeutic targets in breast cancer, and the role of ER in breast cancer.

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For more information, see the Concise Guide to Pharmacology 2017/18: Nuclear hormone receptors.
Full Contents of Concise Guide: http://www.guidetopharmacology.org/index.jsp

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

**3C. 3-Ketosteroid receptors**

- **Agonist**
  - [H]mibolerone
  - [H]methyltrienolone
  - [H]dihydrotestosterone

- **Selective Agonist**
  - [H]galeterone
  - [H]onapristone
  - [H]PF0998425

- **Selective Antagonist**
  - [H]flutamide
  - [H]nilutamide
  - ZK112993
  - bicalutamide

- **Labelled ligands**
  - [H]flutamide
  - [H]nilutamide
  - [H]mibolerone

- **Critical review.**
  - Trends Pharmacol. Sci. 2017
  - Bioorg Chem 2017

- **Comments**
  - Estrogen receptor agonist / antagonist in breast cancer therapy: A critical review.
  - What’s new in estrogen receptor action in the female reproductive tract.

- **Further reading on 3A. Estrogen receptors**
  - British Journal of Pharmacology 2017
  - Trends Pharmacol. Sci. 2017

- **Nomenclature**
  - NR3C1
  - P10275
  - HGNC, UniProt

- **Steroid hormone receptors**
  - Nuclear hormone receptors

- **3C. 3-Ketosteroid receptors**
  - The Concise Guide to Pharmacology 2017
  - Nuclear hormone receptors, S.P.H. Alexander
Mineralocorticoid receptor

Progesterone receptor

Systematic nomenclature
NR3C2
NR3C3
HGNC, UniProt
NR3C2, P08235
PGR, P06401

Rank order of potency

- corticosterone, cortisol, aldosterone [58, 125], progesterone [125]
- progesterone [38]

Selective agonists
- medroxyprogesterone (Affinity at human PR-A) [166], ORG2058, levonorgestrel [9, 128]

Selective antagonists
- finerenone (pIC50 7.7) [20], eplerenone (pK6.9) [5], onapristone (pIC50 6.3) [165], RU28318, ZK112993
- ulipristal acetate (pIC50 9.7) [123], mifepristone (Mixed) (pK9) [167], onapristone (pK7.7) [54], ZK112993

Labelled ligands
- [3H]aldosterone (Selective Agonist) [44, 137] – Rat
- [3H]ORG2058 (Selective Agonist) [166]

Comments:
- [3H]dexamethasone also binds to MR in vitro. Pranogestins have been subdivided into Type I (e.g. onapristone) and Type II (e.g. ZK112993) groups. These groups appear to promote binding of the PR to DNA with different efficacies and evoke distinct conformational changes in the receptor, leading to transcriptional activity, a complex and dynamic interplay of co-regulators and transactivation pathways. These receptors are believed to modulate a diverse range of biological processes.

Further reading on 3C. 3-Ketosteroid receptors