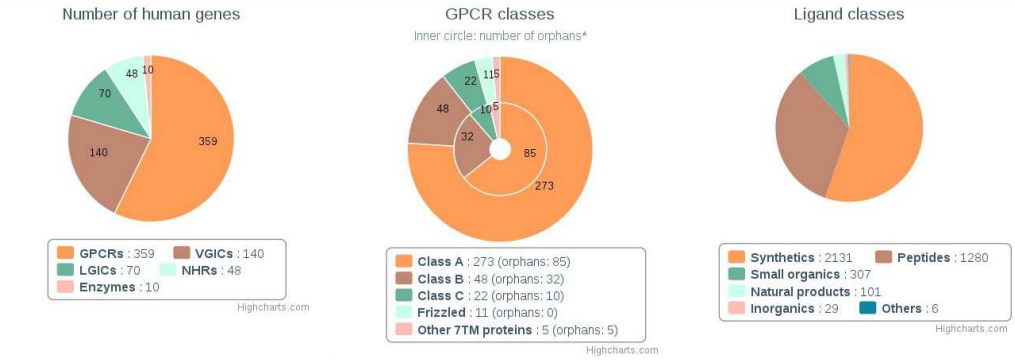
The IUPHAR database

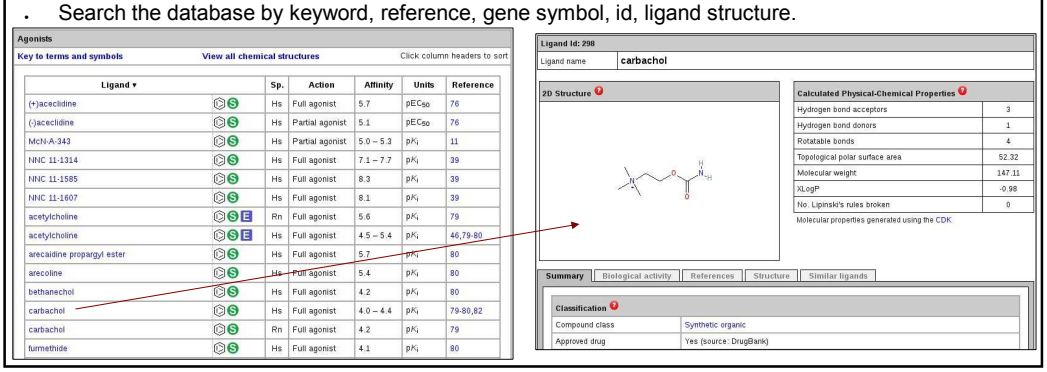
http://www.iuphar-db.org

Email: curators@iuphar-db.org



IUPHAR-DB features include:

- Detailed pharmacological, structural, functional, genomic and physiological information about human and rodent receptors, using IUPHAR-approved nomenclature.
- Content is peer reviewed by members of the IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR); the data are provided through manual curation of the primary literature by a network of over 60 subcommittees.
- Aim is to provide a rigorously curated “gold standard” set of recommended pharmacological tools (licensed drugs, commercially available experimental compounds and radioligands) that have the best profile of “off-target” actions, effectiveness across commonly used experimental species and proven efficacy both in vitro and in vivo.
- Search the database by keyword, reference, gene symbol, id, ligand structure.



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PHARMACOLOGICAL REVIEWS

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International Union of Basic and Clinical Pharmacology. LXXXV: Calcium-Activated Chloride Channels

Fen Huang, Xiuming Wong, and Lily Y. Jan

Department of Physiology, Howard Hughes Medical Institute, University of California, San Francisco, California

BJP British Journal of Pharmacology

Themed Section: Secretin Family (Class B) G Protein-Coupled Receptors – from Molecular to Clinical Perspectives

International Union of Basic and Clinical Pharmacology Review

Pharmacology and functions of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide: IUPHAR Review 1

Anthony J Harmar[1], Jan Fahrenkrug[2], Illana Gozes[3], Marc Laburthe[4], Victor May[5], Joseph R Pisegna[6], David Vaudry[7], Hubert Vaudry[7], James A Waschek[8] and Sami I Said[9]

GPR183 (EBI2) & oxysterols.

Statement by NC-IUPHAR on GPR183 (EBI2)

"Two independent reports (1, 2) propose 7α, 25-dihydroxycholesterol (7α,25-OHC) as an endogenous ligand of this receptor. 7α,25-OHC is synthesised from cholesterol by the sequential action of cholesterol 25-hydroxylase (CH25H) and CYP7B1 (25-hydroxycholesterol 7-α-hydroxylase). Consistent with 7α,25-OHC as an endogenous ligand, inhibition of CYP7B1 with clotrimazole reduced the content of 7α,25-OHC in the mouse spleen and mimicked the phenotype of pre-activated B cells from EBI2-deficient mice (2) and mice deficient in CH25H had a similar phenotype to EBI2 knockout mice."

1. Hannedouche S, Zhang J, Yi T, Shen W, Nguyen D, Pereira JP, Guerini D, Baumgarten BU, Roggo S, Wen B, Knochenmuss R, Noël S, Gessier F, Kelly LM, Vanek M, Laurent S, Preuss I, Miault C, Christen I, Karuna R, Li W, Koo DI, Suply T, Schmedt C, Peters EC, Falchetto R, Katopodis A, Spanka C, Roy MO, Detheux M, Chen YA, Schultz PG, Cho CY, Seuwen K, Cyster JG, Sailer AW. (2011) Oxysterols direct immune cell migration via EBI2. *Nature.* **475** (7357): 524-7. [PMID: 21796212]
2. Liu C, Yang XV, Wu J, Kuei C, Mani NS, Zhang L, Yu J, Sutton SW, Qin N, Banie H, Karlsson L, Sun S, Lovenberg TW. (2011) Oxysterols direct B-cell migration through EBI2. *Nature.* **475** (7357): 519-23. [PMID: 21796211]

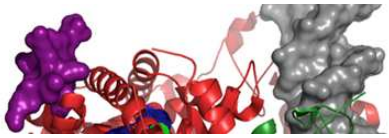
Crystal structures of the μ and κ opioid receptors

Comments by Brian M. Cox:

It is now almost 60 years since Beckett and Casy first proposed that morphine and related drugs must act through a specific receptor in brain to induce analgesia (1), and nearly 40 years since three groups independently showed the presence of high affinity binding sites for such drugs in the central nervous system (2, 3, 4). Another milestone in our understanding of the actions of morphine like drugs comes with the publication this month of the crystal structures of two of the four closely related opioid peptide receptors, the κ opioid receptor (5) and the μ opioid receptor (6). Morphine and other opiates used therapeutically act predominantly through the μ receptor while the κ receptor is activated predominantly by some ketocyclazocines, by the hallucinogenic agent salvinorin A, and by the endogenous opioid dynorphin.

The new reports follow closely on reports earlier this year of other GPCRs. The two groups responsible for these latest developments used similar strategies; the receptors were crystallized as complexes with very tightly binding highly receptor-type-selective antagonist ligands; JDTic in the case of the κ receptor and β-FNA for the μ receptor. Thus in each case the receptor is visualized in an inactive conformation. Nevertheless, some interesting features are immediately apparent. Both receptors crystallized as dimers, with more than one potential interface between adjacent receptor monomers as possible dimerization sites. Higher polymerization states and heterodimerization with other GPCRs are possible. These observations provide a structural basis for earlier proposals that opioid receptors might function as dimers or higher polymers (7). Opiate drugs are also known for their rapid reversibility - the immediacy of the reversal of opiate-induced respiratory depression by naloxone can be dramatic. The new studies show that the ligand binding pockets of both the μ and κ receptors are unusually exposed or open relative to other GPCRs. The accessibility of the binding pocket favors rapid dissociation (except in the case of irreversible antagonists such as β-FNA). Since the affinity of many agonist and antagonists at μ or κ receptors is high despite their rapid reversibility, their association rates must also be very high.

Another feature of opioid receptors is the apparent ability of different ligands acting through the same receptor type to direct signaling through different effector pathways. Ligands for opioid receptors are chemically very heterogeneous. The reported structures for the μ and κ receptors point to accessory sites around the common ligand binding pocket for each receptor that provide additional points of receptor interaction for some ligands. Much work needs to be done to understand the basis of agonism at these receptors, but it is tempting to speculate that these additional interaction sites for some ligands might be exploited in the design of agonists preferentially driving signaling through alternative transduction pathways.



Guide to PHARMACOLOGY

http://www.guidetopharmacology.org

A new collaboration between IUPHAR and the British Pharmacological Society (BPS).

The Guide to Pharmacology is intended to become a "one-stop shop" source of quantitative information on drug targets and the prescription medicines and experimental dugs that act on them.

It provides a single entry point to a database of information from the 5th edition of the BPS Guide to Receptors and Channels (GRAC) and the IUPHAR database.

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Guide to Pharmacology features include:

- Succinct overview of the key properties of >1600 established or potential human drug targets.
- Background reading, expert summaries, recommended agonists and inhibitors.
- Links to detailed information and ligand lists in IUPHAR-DB.
- Fully searchable by keyword, gene symbol, ligand and reference.