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Opioid receptors: Structural and mechanistic insights into pharmacology and signaling

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ABSTRACT

Opioid receptors are important drug targets for pain management, addiction, and mood disorders. Although substantial research on these important subtypes of G protein-coupled receptors has been conducted over the past two decades to discover ligands with higher specificity and diminished side effects, currently used opioid therapeutics remain suboptimal. Luckily, recent advances in structural biology of opioid receptors provide unprecedented insights into opioid receptor pharmacology and signaling. We review here a few recent studies that have used the crystal structures of opioid receptors as a basis for revealing mechanistic details of signal transduction mediated by these receptors, and for the purpose of drug discovery.

1. Introduction

Opioid receptors belong to the super-family of G-protein coupled receptors (GPCRs), which are by far the most abundant class of cell-surface receptors, and also the targets of about one-third of approved/marketed drugs (Vortherms and Roth, 2005). Residing in different parts of the body (e.g., brain, spinal cord, digestive tract, etc.), opioid receptors are widely studied due to their crucial role in pain management (Pasternak, 2014), drug abuse/addiction (Kreek et al., 2012), and mood disorders (Lutz and Kieffer, 2013). There are three major subtypes of opioid receptors: δ receptor, μ receptor, and κ receptor. These receptors are activated by endogenous peptides such as endomorphins, enkephalins, and dynorphins, but also by naturally occurring alkaloids and other semi-synthetic and synthetic small-molecule ligands (McCurdy et al., 2003). Although a fourth receptor subtype, i.e., the nociceptin opioid receptor (NOP receptor), is phylogenetically related to δ receptor, μ receptor, and κ receptor, it does not bind the same ligands.

In addition to their still unbeatable analgesic effects, opioid drugs are accompanied by a variety of undesirable side effects, including vomiting, nausea, constipation, tolerance, addiction etc. (Feng et al., 2012). Thus, substantial drug discovery efforts have been devoted over the years to reduce the disadvantages of these drugs while retaining their therapeutic efficacy. In the absence of high-resolution crystal structures of opioid receptors until 2012, the majority of these efforts used ligand-based strategies, although some also resorted to rudimentary molecular models of the receptors based on relatively distant structural templates. Notwithstanding this substantial amount of work over the course of several years, safe and effective opioid ligands remain the holy grail of the pharmaceutical industry.

The recent advances in membrane protein crystallization (Chun et al., 2012), which enabled the determination of various high-resolution crystal structures of GPCRs, including those of all four opioid receptor subtypes (Fenalti et al., 2014; Granier et al., 2012; Manglik et al., 2012; Thompson et al., 2012; Wu et al., 2012) (see Fig. 1), marked the beginning of a new era in opioid research. By revealing important details of ligand–receptor interactions at the orthosteric binding site (i.e., the site at which endogenous opioid ligands bind), or allosteric sites (e.g., the much anticipated sodium binding site (Fenalti et al., 2014)), these structures evidently offer new opportunities for drug discovery at opioid receptors (Filizola and Devi, 2013). Notably, comparison between the four opioid receptor crystal structures (Filizola and Devi, 2013) reveals common ligand–receptor interactions that may be responsible for the molecular recognition of classical opioid drugs. In contrast, the different ligand–receptor interactions that are mostly located at the extracellular side of the receptor may be responsible for the

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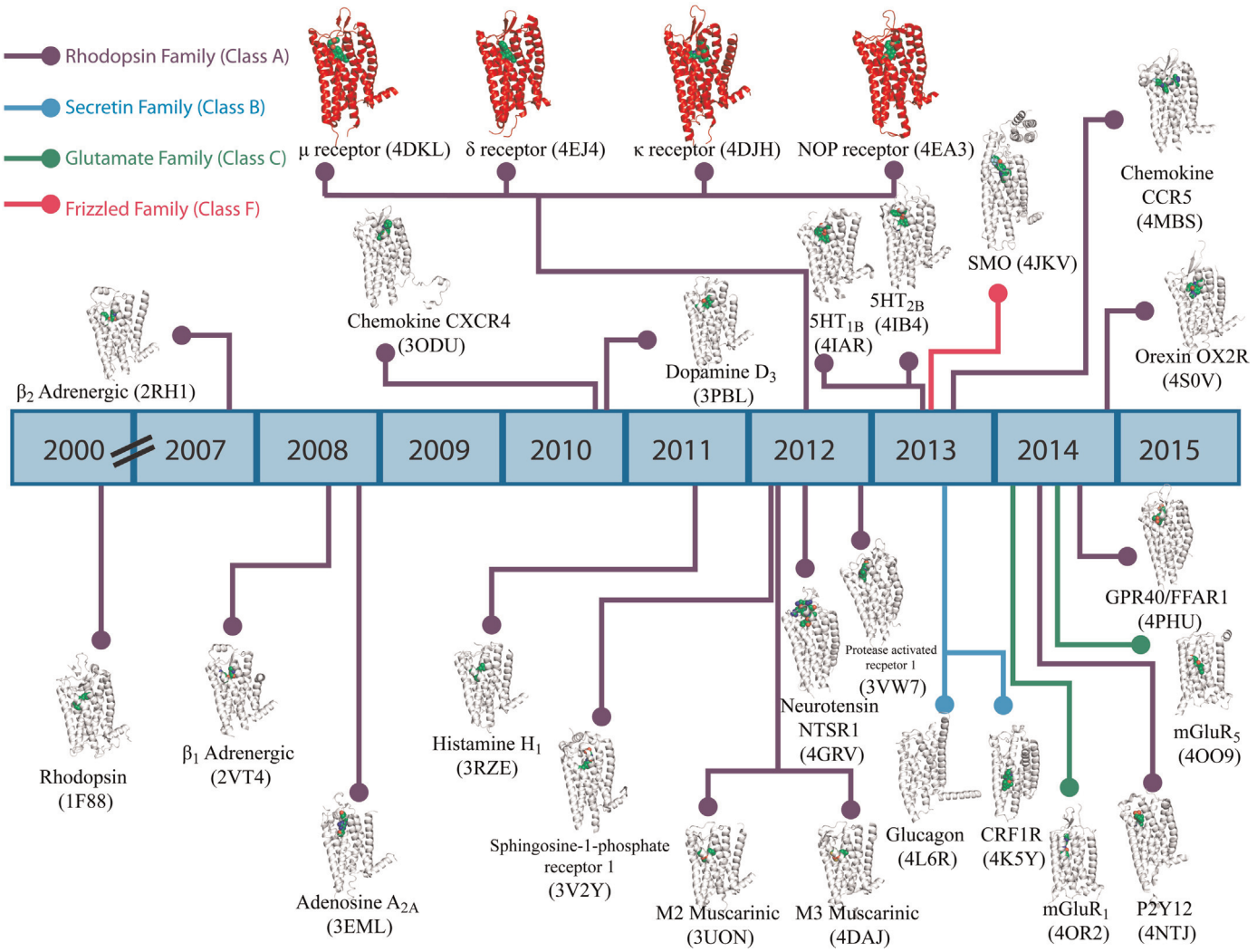

Fig. 1. Time-line of representative crystal structures of GPCR subtypes. Each representative crystal structure is shown in cartoon representation, with the bound ligand shown as colored spheres. With the exception of opioid receptors, which are colored in red, all the others are depicted in silver. Rhodopsin, Secretin, Glutamate, and Frizzled subfamilies of receptors are indicated with purple, cyan, green, and magenta colors, respectively. PDB IDs of the crystal structures are included in parenthesis after each protein name. Specifically, the reported crystal structures are (in chronological order): rhodopsin (1F88 (Palczewski et al., 2000)), β_2 Adrenergic (2RH1 (Cherezov et al., 2007)), β_1 Adrenergic (2VT4 (Warne et al., 2008)), Adenosine A_{2A} (3EML (Jaakola et al., 2008)), Chemokine CXCR4 (3ODU (Wu et al., 2010)), Dopamine D_3 (3PBL (Chien et al., 2010)), Histamine H_1 (3RZE (Shimamura et al., 2011)), Sphingosine-1-phosphate receptor 1 (3V2Y (Hanson et al., 2012)), M2 Muscarinic (3UON (Haga et al., 2012)), M3 Muscarinic (4DAJ (Kruse et al., 2012)), Neurotensin NTSR1 (4GRV (White et al., 2012)), μ receptor (4DKL (Manglik et al., 2012)), δ receptor (4EJ4 (Granier et al., 2012)), κ receptor (4DJH (Wu et al., 2012)), NOP receptor (4EA3 (Thompson et al., 2012)), Protease activated receptor 1 (3VW7 (Zhang et al., 2012)), $5HT_{1B}$ (4IAR (Wang et al., 2013a)), $5HT_{2B}$ (4IB4 (Wacker et al., 2013)), SMO (4JKV (Wang et al., 2013b)), Glucagon (4L6R (Siu et al., 2013)), CRF1R (4K5Y (Hollenstein et al., 2013)), Chemokine CCR5 (4MBS (Tan et al., 2013)), mGluR1 (4OR2 (Wu et al., 2014)), P2Y12 (4NTJ (Zhang et al., 2014)), $mGluR_5$ (4OO9 (Dore et al., 2014)), GPR40/FFAR1 (4PHU (Srivastava et al., 2014)), and Orexin OX2R (4S0V (Yin et al., 2014)).

specificity of the ligands for a given receptor subtype. Among them are the interactions crystallographic ligands of μ receptor and δ receptor form with residues of the transmembrane (TM) helices TM6 and/or TM7, or those that the crystallographic ligands of κ receptor and NOP receptor form with TM2 and TM3 residues.

Additional, important details of opioid receptor binding and signaling were provided by the ultra-high resolution crystal structure of δ receptor (Fenalti et al., 2014), which only recently appeared in the literature. In particular, this structure revealed the presence of an allosteric binding site occupied by sodium, which had been suggested to serve as an allosteric modulator of opioid receptors for quite some time (Pasternak and Snyder, 1975), and was recently found in ultra-high resolution crystal structures of other GPCRs (Katritch et al., 2014; Liu et al., 2012). In all these ultra-high resolution crystal structures, this ion is located near the conserved D2.50 residue, which is about 10 Å below the D3.32 residue that interacts with several orthosteric ligands of GPCRs, including classical opioid ligands (note that all the residues mentioned in this manuscript are numbered according to the Ballesteros–Weinstein generic numbering scheme (Ballesteros and Weinstein, 1995)).

Although a detailed knowledge of the crystal structures of opioid receptors provides a new dimension for structure-guided drug discovery efforts, the realizations that these receptors are rather dynamic systems and that several opioid ligands can activate multiple signaling pathways add another level of complexity to an already complicated problem. Various cases of so-called functional selectivity or biased agonism, primarily through $G_{i/o}$ or arrestin, have been reported in the literature for all major opioid receptors (e.g., see (Luttrell, 2014; Thompson et al., 2014, 2015; Violin et al., 2014) for recent reviews). This selectivity in opioid receptor signaling and function may be achieved through (i) conformational preferences induced by ligands with different efficacies binding at the orthosteric site and inducing coupling of

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