REVIEW ARTICLE

G Protein Coupled Receptors in Drug Development: Unveiling the Role of the Orphan GPCRs

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Abstract

G protein-coupled receptors (GPCRs) represent the largest superfamily of cell emphasizing that they represent an important area that could play a significant role in future pharmacological research and therapeutic discovery. Surface membrane receptor and are encoded by approximately 1000genes.Theyplayacrucial role in various physiological processes and are among the most common drug targets. This study provides a comprehensive overview of the current understanding and advancements in GPCR research, with a particular focus on orphan GPCRs. The document begins by introducing the structural and functional aspects of GPCRs, highlighting their diversity and the importance of recent breakthroughs in structural biology techniques, such as X-ray crystallography and cryo-electron microscopy. It then delves into the historical development of the receptor concept and the discovery of GPCRs, tracing the evolution of our understanding of their signaling mechanisms. A significant portion of the study is dedicated to the exploration of orphan GPCRs, which are a subset of GPCRs that lack identified endogenous ligands. The document discusses the challenges and opportunities associated with these receptors, including their potential as novel drug targets, their involvement in diverse disease states, and the innovative approaches being employed to deorphanize and characterize them. The study also examines emerging trends in GPCR research, such as the utilization of allosteric modulators, biased signaling, and the integration of computational methods like machine learning. These advancements hold promise for enhancing our understanding of GPCR function and facilitating the development of more selective and effective therapeutic agents. Overall, this comprehensive review highlights the pivotal role of GPCRs in drug development and the significant potential of orphan GPCRs as a frontier for future pharmacological research and therapeutic discoveries.

Keywords: GPCRs (G protein-coupled receptors), Orphan GPCRs, Drug targets, Structural biology, Signaling mechanisms
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Introduction

G protein-coupled receptors (GPCRs) are the largest superfamily of cell surface membrane receptor sandareen coded by approximately 1000genes, sharing conserved seven-transmembrane (7TM) helices connected by three intra-and three extra-cellular loops.[1] The family of G-protein coupled receptors (GPCRs) represents the largest class of receptors in the human genome and some of the most common drug targets. Located on the cell membrane, they transduce extracellular signals into key physiological effects. Natural GPCR ligands include neurotransmitters, chemokines, hormones, odour or photons. [2, 3] Emerging knowledge of the structure and physiological functions of GPCRs has begun to alter the approaches to GPCR drug discovery. Traditional efforts have focused on targeting the ortho steric binding sites of GPCRs where the endogenous ligands bind to elicit signal transduction. This approach yields compounds that either directly activate the target GPCR (agonists) or block the actions of the endogenous ligand (antagonists or inverse agonists). The past decade has witnessed a pronounced increase in the pursuit of allosteric ligands that influence receptor activity by binding to sites that are topographically distinct from the orthosteric binding site[4,5]. Roughly 350 receptors have the potential to be druggable, yet the physiological function and endogenous ligand of roughly 100 so-called orphan receptors are still unknown. GPCRs area very attractive class of pharmaceutical targets because of the possibility of having a molecular switch a than that initiates a signaling cascade in the cell interior, as well as the diverse distribution of GPCRs in different tissues. An estimated 50% of all modern medicine are thought to interact with GPCRs. proving that the pharmaceutical industry has been effective in pursuing this class of receptors. GPCRs are transmembrane proteins, as their function suggests, which makes structure elucidation far more challenging than for globular proteins [6].

Structure of GPCR

The crystal structure of bovine rhodopsin was the first atomic-resolution GPCR structure discovered in 2000. It took almost another decade until the first diffusible ligand-bound structures were published. The development of techniques to receptor stabilization, including as thermo-stabilization, fusion proteins, and high-affinity ligands, enabled the determination of GPCR structures. These approaches have transformed GPCR structural biology, yielding more than 500 receptor crystal structures. Since 2017, cryo-electron microscopy (cryo-EM) has been utilized to resolve GPCR structures [11]. Cryo-EM is a novel approaching GPCR structural biology that enables direct viewing of detergent- or nano disc-solubilized GPCRs. This enables the identification of intractable completely active state and bigger protein complexes, such as GPCR-G protein complexes. The number of cryo-EM structures showing GPCRs in complex with intracellular partners has increased enormously [15].

GPCRs are divided into six classes based on amino acid sequence similarities, with only four of the classes found in humans. Class A (rhodopsin like) contains the largest number of GPCRs (719inhumans), with about half being sensory receptors involve. In smell or vision. Approximately 350 non-sensory receptors are activated by diffusible ligands like hormones or neurotransmitters and contain many well-characterized drug targets [17]. Class B receptors (48in humans) are divided into two sub classes: secretin and adhesion receptors. The secretin sub-class has a large extracellular domain for binding peptide ligands, while the glucagon-like peptide receptor GLP1R is a well- characterized target for diabetes treatment [18]. Class C receptors form stable dimers essential for receptor signaling, while other classes are believed to be signaling- competent as monomers [19]. Metabotropic glutamate receptors (mGluRs) are archetypal members of class C with a large extracellular domain that binds agonists, targeting various disease settings like schizophrenia, depression, and movement disorders [20, 21]. Class F receptors (11 members in humans) contain frizzled and smoothened receptors, which can be activated by steroids and small molecules for cancer treatment [22, 23].

Ligands are depicted as space filling models; orthosteric ligands (gray) negative allosteric modulators (purple), positive allosteric modulators (magenta). For Glp1R, the native agonist can be co crystallized with just the extracellular domain (ECD; top) while a truncated peptide that binds only to the transmembrane portion of the receptor is sufficient for receptor activation. PDBIDs are shown for all the structure depicted and subunits of the heterotrimeric G proteins are indicated [16].

History Of GPCR

The study of receptors began with Paul Ehrlich and John Langley in the early 1900s, who developed a theory of side-chains, structures on the surface of cells capable of binding to certain toxins [24, 25]. John N. Langley later coined the term receptive substance in1905while studying muscle cell contractions stimulated by nicotine [26]. These early ideas led to the initial proposal of the receptor concept, which postulated that receptors interact with external chemical stimuli and relay these responses to effectors within the cell, generating physiological changes in response [27]. Despite the later-proven accuracy of this theory, the existence of receptors remained highly contentious for decades. Sir Henry Dale, a Nobel Prize-winning scientist, and Raymond

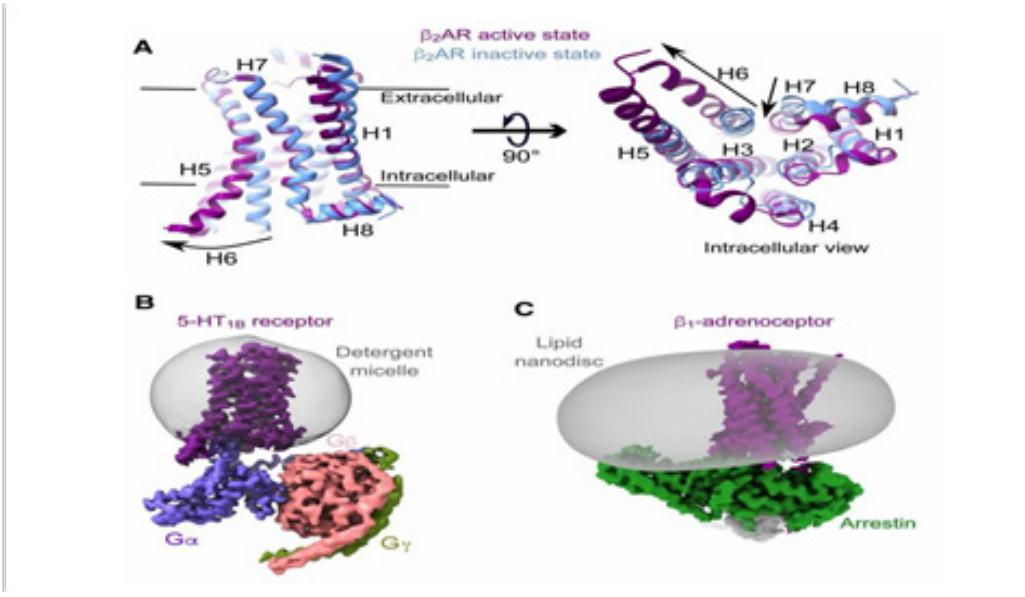

Figure1: GPCR (A) Cartoon representation of the β_2-adrenergic receptor (β_2AR), illustrating the conformational transition from the inactive state (blue; PDB ID: 2RH1) to the active state (purple; PDB ID: 3SN6) upon coupling to a G protein (not shown).(B) Cryo-EM density map of the serotonin 5-HT_1B receptor in complex with a heterotrimeric G protein, highlighting receptor–G protein interactions.(C) Structure of the β_1-adrenergic receptor bound to arrestin, stabilized in a lipid nano disc environment, illustrating GPCR coupling to arrestin-mediated signaling pathways.

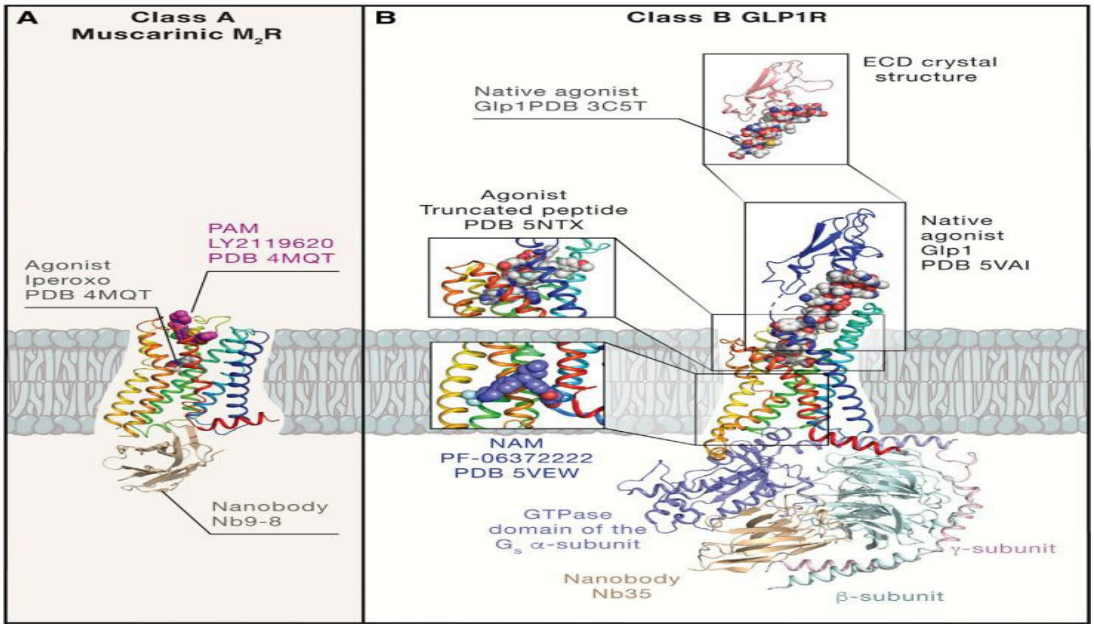

Figure 2: Diversity of GPCR Structures from Different Classes (A–D) Structures are depicted for receptors from class A (A2AR) (A), class B (Glp1 receptor) (B), class C (metabotropic glutamate receptor mGlu5) (C), and class F(smoothened) (D).

Ahlquist, a distinguished pharmacologist, both believed that α and β receptors did not exist [28]. The 1955 edition of The Pharmacological Basis of Therapeutics states that these quotes illustrate the dogma in the field at the time [29].

An understanding of the physicochemical basis of ligand binding to receptors began to emerge after Langley's initial work, leading to the development of receptor theory. Through the work of Hill, Clark, and others, physicochemical models for understanding ligand binding to receptors emerged by developing quantitative relationships between drug action and changes in physiology [30, 31]. Insights into the mechanisms of drug action started to change with the discovery of intracellular signaling pathways regulated by receptors. Research from Earl Sutherl and Jr.'slab first showed that the activity of β- adrenoreceptors resulted in the production of a second messenger, cAMP, which was later shown to be produced by AC (adenylyl cyclase). Martin Rodbell's lab determined that Activation by hormones required the presence of guanosine triphosphate (GTP), possibly through the association of an intermediary protein that bound GTP. Alfred Gilman's lab successfully identified and isolated the intermediary heterotrimeric G- protein [30].

The crystal structure of bovine rhodopsin was the first GPCR structure to be determined at atomic resolution in 2000 [11]. In the b2 adrenergic, b1 adrenergic, and A2A adenosine receptors, the first diffusible ligand-bound structures were reported in 2000 and 2007. High-resolution diffraction was initially hindered by the low expression of membrane protein GPCRs and their conformational flexibility. Protein engineering and X-ray crystallography techniques have advanced over the last 20 years, yielding a multitude of antagonist- or agonist-bound GPCR structures [1]. The first GPCR-G protein complex was determined in 2011 using X-ray diffraction [33], but the demanding nature of X-ray crystallography has made crystallization difficult. Cryo-EM. Hasemergedasan alternative technique, all owing for direct visualization of detergent- ornanodisc-solubilized GPCRs, enabling the determination of larger protein complexes and fully active states [15].

However, both crystallography and cryo-Emare limited to capturing stable and lowest energy conformation sunder crystallization conditions.[34] Advanced XFEL shave the potential to solve this issue, allowing for atomic-level information at femtosecond timescales. [35] NMR spectroscopy, DEER spectroscopy, and FRET provide valuable data on the number of states and the irrelative populations [36,37]. Molecular dynamics simulations offer a comprehensive view of complete protein structures, capturing intermediate states along the transition pathway [38]. Advances in structural biology of GPCRs have revealed key information on ligand-receptor interactions, conformational changes, and signaling complexes, opening opportunities for exploration of receptor activation, orthosteric/allosteric modulation, biased signaling, and dimerization [39, 40].

Mechanism Of Gpcr

GPCRs, when activated by ligands or light, trigger a series of biochemical processes called receptor desensitization, sequestration/ internalization, and downregulation to attenuate GPCR signals. Desensitization occurs within second so agonist exposure and is caused by receptor phosphorylation. Second messenger-activated protein

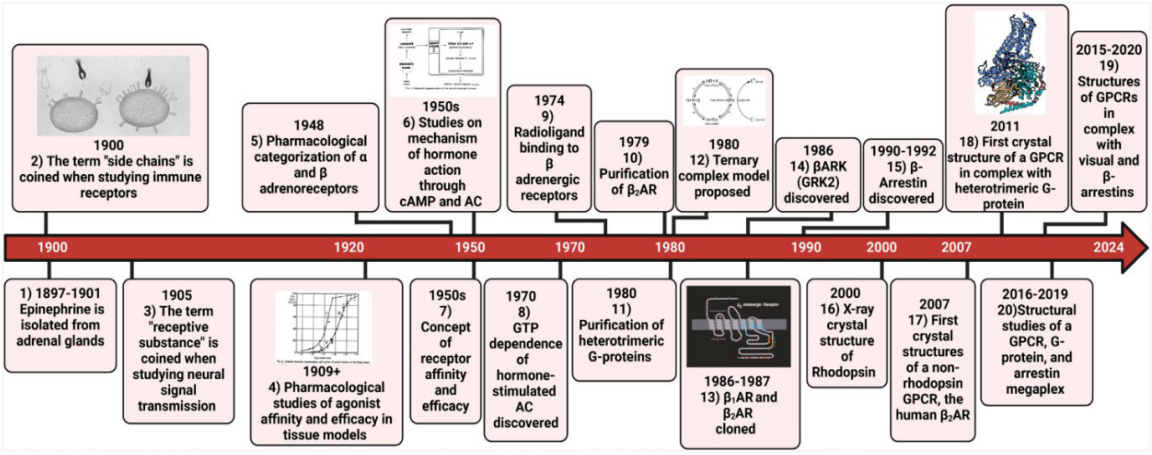

Figure 3: History of GPCR [32].

kinases, such as PKA and PKC, phosphorylate serine and threonine residues in GPCR's cytoplasmic loops and C-terminal tail domains, reducing receptor-Gprotein binding. effectiveness and signaling. Desensitization doesn't affect the number of receptors in cells and is quickly restored when agonists are removed [12, 13].

GPCRs undergo internalization, as lower process than desensitization, several minutes after agonist exposure. Most GPCRs are sequestered in a dynamin-dependent manner, requiring a major GTPase for clathrin-coated vesicles to separate from the plasma membrane. GRK-mediated GPCR phosphorylation and β-arrestin receptor binding promote clathrin-dependent endocytosis. Tore-sensitize a sequestered GPCR, separate β-arrestin, dephosphorylate the receptor, and remove the attached ligand. Prolonged activation leads to down regulation, achieved through endocytosis. Many GPCRs undergo ligand-induced endocytosis via clathrin-coated m pits, mediated by beta-arrestins [14].

Role of GPCR in cellular signaling

G protein-coupled receptors (GPCRs) are thought to affect the entire cell uniformly, with their second messengers, cAMP, IP3, and Ca2+, being water-soluble and freely diffusible. However, evidence suggests that these assumptions are often incorrect. Receptors may be concentrated in distinct locations on the cell surface or in cell organelles, and concentrations of cAMP and Ca2+ may show subcellular gradients. Signaling via spatially confined calcium signals is well understood, with abundant Ca2+-binding proteins providing high buffering capacity. Evidence for cAMP buffering is lacking, but recent evidence indicates a conspicuous intracellular buffering capacity for cAMP, making it largely immobile in unstimulated cells. The compartmentalized nature of cAMP signaling and GPCR signaling across multiple effectors and cellular locations has transformed our understanding of how these receptors function. [7]. An activated receptor can interact with heterotrimeric G protein complexes. Receptors function as guanine nucleotide exchange factors (GEF) to promote dissociation of GDP from the Gα subunit in exchange for GTP (figure 2A). Alternatively, GPCR activation can occur through interaction with adaptor and scaffolding proteins. Through specific binding sites, adaptor/scaffolding proteins, such as A kinase anchoring proteins (AKAP) and β-arrestins (figure 2B), mediate interactions between the receptor and downstream second messengers by scaffolding a network of proteins which then operate as a large molecular complex [8]. Receptor signaling is modulated by various mechanisms to control cellular functions. Three such processes are highlighted here - deactivation, desensitization, and receptor internalization [9]. In other cases of continuous agonist stimulation, the receptor can be phosphorylated by downstream second-messenger protein kinases or a family of G protein-coupled receptor kinases (GRK). Following phosphorylation, β-arrestin is recruited to their receptor leading to the inhibition of receptor-G protein interaction via steric hindrance [10]

This association triggers activation of the ERK (MAPK) cascade leading to cytosolic signaling pathways. Figures 2A and 2B were adapted from Pierce, et al. [8]

Orphan Receptor

There are more than 200 human GPCRs identified with their physiological ligands. Still, about 120 GPCRs have not yet been identified as endogenous ligands. These so- called orphan GPCRs represent an unexplored area of GPCR drug discovery [41]. Orphan G protein-coupled receptors (o GPCRs) represent a specific subset of GPCRs that still elude the identification of their endogenous ligands [42]. While there has been considerable advancement in the structural and pharmacological research of GPCRs, the characterization of oGPCRs remains somewhat limited, and therefore rather perplexing. Never the less, it is worthwhile to note that GPCRs play a multitude of diverse roles in the central nervous system, offering tantalizing new prospects for drug discovery as a prospective reservoir of drug targets [43].

Orphan G protein-coupled receptors (GPCRs) are a subset of the GPCR superfamily that lack identified endogenous

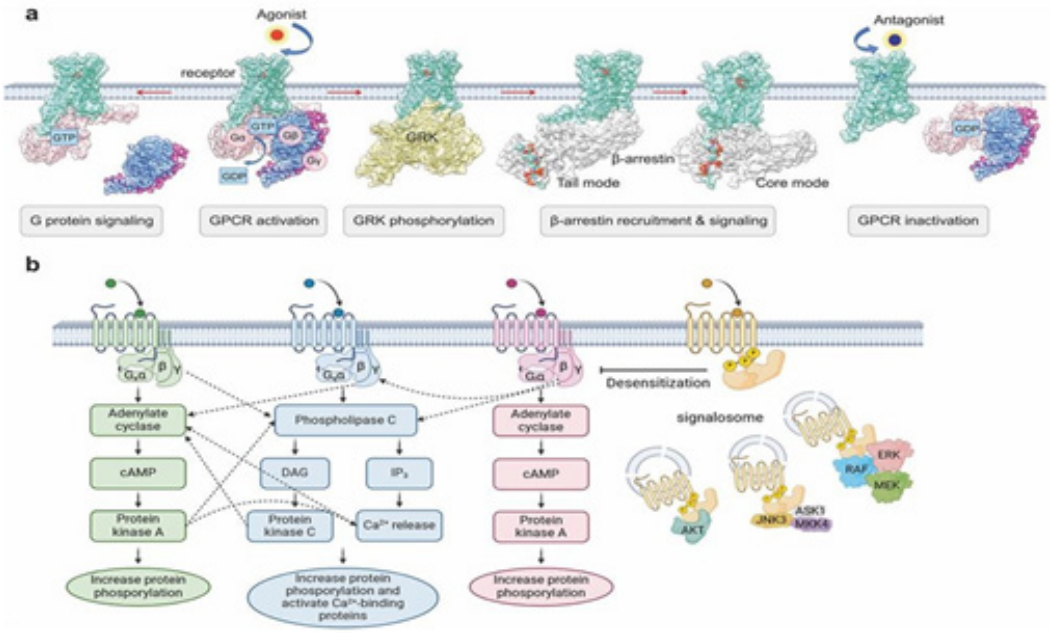

Figure 4: a. Schematic representation of GPCR activation process. Upon agonist (red circle) binding, the receptor proceeds into a pre-activation state coupling with the G protein heterotrimer, where the exchange of GDP and GTP in Gprotein α subunit leads to G protein dissociation and mediate G protein signaling pathway. The phosphorylation of the receptor C-terminal tail by GRK binding promotes arrestin recruitment and signaling. When the antagonists (blue circle) bind, the receptor stabilizes in an inactive state. **b.** Crosstalk of downstream pathway of Gs, Gq, Gi and arrestin [1]

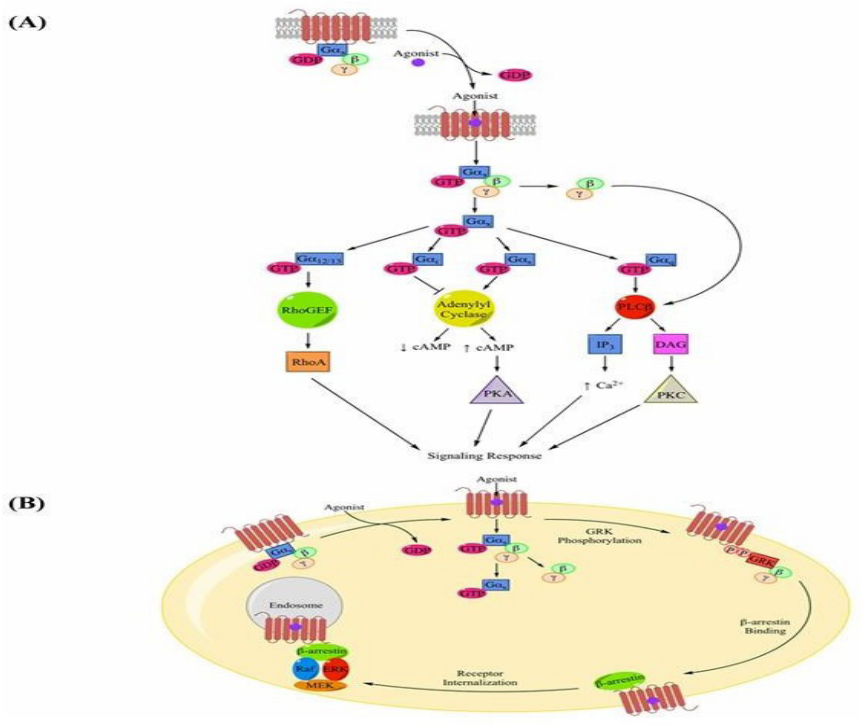

Figure 5: (A) A classic example of GPCR signaling pathway. Receptors, such as ADRB2, are in an inactive state until an agonist binds to activate the receptor. The activated receptor-Gprotein complex is formed resulting in GDP to GTP exchange by the G protein complex followed by the dissociation of the Gα subunit from the Gβγ dimer. Both Gα and Gβγ subunits, in turn, activate downstream effectors. Gαx represents the general Gα subunit followed by diagrams for Gα12/13, Gαi, Gαs, and Gαq pathways. (B) β-arrestins can function as adaptor/scaffolding molecules activating the ERK (MAPK) cascade. GRK phosphorylates the activated receptor recruiting β- arrestin to the phosphorylation site sa long with Raf, ERK (MAPK), and MEK.

Table1: Key milestones in discovery of orphan GPCRs

Year	*Milestone*	*Description*
1986	Concept of GPCRs Established	The β2-adrenergic receptor and opsins were identified as sharing a seven-transmembrane domain topology, leading to the classification of GPCRs as a supergene family.
1987	First Orphan GPCR Reported	G-21 was reported as the first orphan GPCR, establishing the groundwork for future research into orphan receptors.
1988	First Deorphanizations	The serotonin 5-HT1 A receptor and dopamine D2 receptor were deorphanized using reverse pharmacology, marking a significant advancement in understanding orphan GPCRs.
1989	Introduction of PCR- Based Screening	PCR-derived techniques were introduced for discovering orphan GPCRs, allowing for rapid identification of novel receptors.
1990s	High-Throughput Screening Techniques Developed	High-throughput assays for monitoring second messenger responses were developed, enhancing the ability to characterize orphan GPCRs pharmacologically.
2000	Publication of Bovine Rhodopsin Structure	The first crystal structure of a GPCR, bovine rhodopsin, was published, providing insights into GPCR architecture and function.
2007	Structure of Human β2-Adrenergic Receptor	The resolution of the human β2-adrenergic receptor structure further advanced the understanding of GPCRs and facilitated ligand identification efforts.
Early 2010s	Identification of Novel Ligands for Orphan GPCRs	Several novel neuropeptides, including orexin and prolactin-releasing peptide, were identified as ligands for orphan GPCRs through advanced screening methods, demonstrating the potential for discovering new signaling pathways.
2020	Advances in Single- Cell RNA Sequencing	Techniques such as single-cell RNA sequencing were employed to explore orphan GPCR functions in various physiological contexts. For example, GPR87 was identified as a biomarker in idiopathic pulmonary fibrosis.
Ongoing	Continued Exploration and Deorphanization Efforts	Research continues to focus on deorphanizing remaining orphan GPCRs, with over 140 orphan GPCRs still lacking identified ligands. Advances in structural biology and computational modeling are expected to facilitate future discoveries.

ligands. These receptors were initially discovered through molecular biological analyses and have since become central to the field of reverse pharmacology, where researchers aim to match these receptors with potential transmitters [44, 45]. The identification and study of orphan GPCRs have been significantly advanced by high-throughput screening technologies, leading to the de orphanization of numerous receptors and the discovery of novel neuropeptides [44].

The therapeutic potential of orphan GPCRs is immense, given their widespread distribution and involvement in various physiological processes. Despite their promise, the development of therapeutic compound targeting these receptors has been low due to the challenges in studying them. Recent advancement in protein crystallography and homology modeling have improved the identification of therapeutics targeting these receptors. The increasing number of solved GPCR structures has enhanced the accuracy of homology models, thereby improving the success rates of virtual ligand screens [46, 47].

Orphan GPCRs play crucial roles in various biological systems, including the central nervous system, where they are involved in complex processes such as circadian regulation and stroke pathophysiology [48]. The search for ligands of orphan GPCRs has led to the development of sophisticated structure-based ligand discovery approaches. These methods leverage the growing number of GPCR crystal structures to create homology models, which are then used in virtual ligand screens to identify potential receptor-binding compounds. This approach has been instrumental in exploring the pharmacological potential of orphan GPCRs [47, 49].

History of Orphan GPCRs

Orphan Gprotein-coupled receptors (GPCRs) are a subset of GPCRs that were initially identified without known endogenous ligands. These receptors were discovered through molecular biological analyses and homology screening approaches, which allowed researchers to identify GPCRs based on their genetic sequences rather than their functional characteristics [44, 45]. The term "orphan" refers to the fact that these receptors lacked known natural ligands, making them unique targets for further research and drug discovery. The discovery of orphan GPCRs marked the beginning of a new era in pharmacology known as reverse pharmacology. Traditionally, receptors were characterized by first identifying their natural ligands, or transmitters, and then studying the receptors' pharmacological properties. However, with the advent of molecular cloning techniques in the late 1980s, researchers began identifying GPCRs based on their genetic sequences, even when their natural ligands were unknown [45]. This shift led to the development of reverse pharmacology, where orphan GPCRs were used as targets to identify their endogenous ligands [44, 45]. The evolutionary origin of orphan GPCRs can be traced through phylogenetic classifications based on receptor sequences and ligand binding properties. For instance, a ligand-based

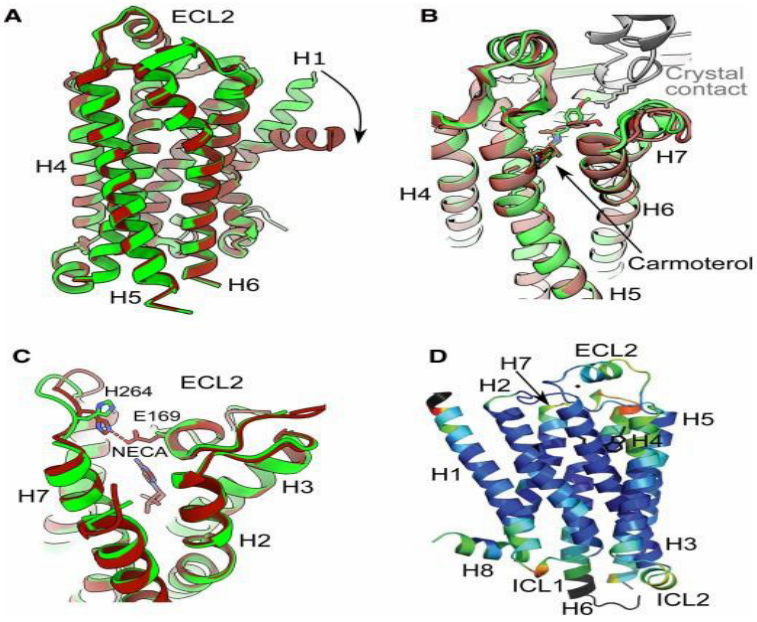

Figure 6: ArtefactsinX-ray crystallography. (A)60° kink of H1 in chain A(brown) of β1AR compared with chain B (green); PDB ID 2VT4. (B) Different pose of the methyl phenoxy moiety of carmoterol in chain A (brown) compared with chain B (green); PDB ID 2Y020. (C) The salt bridge in the extracellular region of A2AR determined in the crystal structure at pH 4.8 (PDB ID 5G53) is absent from the cryo- EM structure determined at pH 7.5 (PDB ID 6GDG). (D) The RMSD differences (rainbow coloration) between β1AR crystallized in detergent (PDB ID 2VT4) compared with β1AR crystallized in lipidic cubic phase (PDB ID 4BVN) were determined and plotted on the structure (red, large differences; dark blue, no differences). Panel 2D has been reproduced from [108].

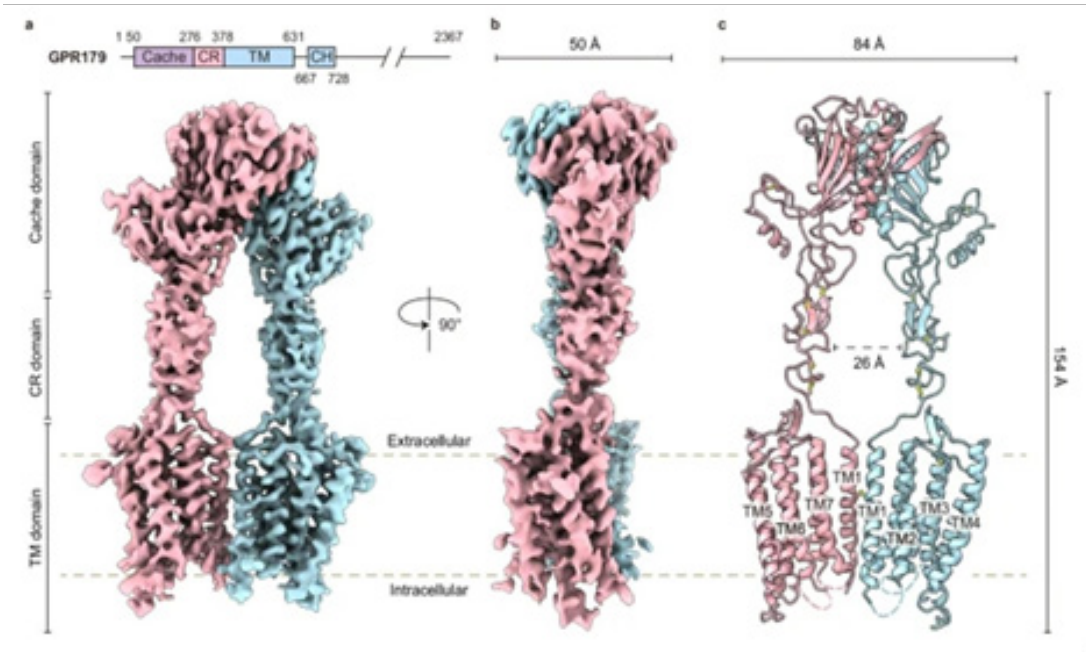

Figure 7: Cryo-EM structure of human GPR179. a Schematic diagram showing the sub domain composition inGPR179 and a cryo-EM map ofGPR179 (front view). The Cache domain, cysteine-rich domain (CR domain), transmembrane domain (TM domain), and cytoplasmic helices (CH) are colored in violet, light pink, and light blue, respectively. Chains A and B are represented as light pink and light blue, respectively. b Cryo-EM map of GPR179(sideview). c Model of GPR179(front view) colored the same as in (a). Transmembrane helices are denoted as TM [58]

Table 2: An overview on the effects of the orphan GPCRs in the modulation of pain and analgesia [109].

Receptor	*Models*	*Gender/ Species*	*Endogenous Ligands or Agonist*	*G Protein Type*	*Distribution*	*Role in Pain*
GPR3 4	SNI	Male/mice	Lyso PS	Gαi	Spinal cord	GPR34is mainly expressed in microglia. GPR34-KO significantly reduces the release of inflammatory factors, leading to pain relief.
GPR3 7	Zymosa n, capsaici n, osteocal cin, chlorog enicacid	Male/mice	ARU, NPD1, TX14, prosaposin, Saposin C	Gαi	Macro-phages	Macrophages express GPR37, which contributes to inflammation relief. NPD1 and TX14 bind to GPR37, eliciting GPR37-
GPR8 5	BCP	Female/rat s	None	None	Spinal cord	BCP upregulates GPR85 expression in spinal dorsal horn neurons. Inhibition of GPR85 by miR143 alleviates mechanical pain sensitivity in rats.
GPR1 32	SNI, CIPN	Male/mice	9-HODE,13- HODE	Gαq	Macro phages	Knock out of GPR132 diminishes SNI-induced mechanical pain sensitivity and reduces secretion of TNFα, IL-6,and VEGF.
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GPR1 32	SNI, CIPN	Male/mice	9-HODE,13- HODE	Gαq	Macro phages	Knock out of GPR132 diminishes SNI-induced mechanical pain sensitivity and reduces secretion of TNFα, IL-6,and VEGF.
GPR1 51	SNI, CCI, pIONT, SNL	Male/mice	None	Gαi	DRG, Spinal cord	GPR151gene mutations have no effect on SNI- induced mechanical pain sensitivity.Knockout of GPR151 reduces inflammatory molecule release and mitigates neuropathic pain.
GPR1 60	CCI/SN I/ SNL	Female/M ale rat	CARTp	Gαi	Spinal cord	Elevated GPR160 expression in the dorsal horn of the spinal cord is involved in neuropathic pain via the ERK signaling pathway. Pain may be relieved by intrathecal siRNA.

Cont...

GPR171	CFA/C CI/ PINP	Male/mice	BigLEN	Gαi	DRG	GPR171 modulates noxious ion channels to weaken pain signaling. Analgesic effects observed in male mice with MS15203.
GPR177	CCI	Female/M ale mice	None	None	DRG	GPR177is expressed in class A neurons with large diameters in the dorsal root ganglion. It plays a role in synaptic transmission and plasticity modulation.
GPR183	Neuropathic pain	Female/Male mice	7α,25-OHC	Gαi	Spinal cord	GPR183 Mediates pain signaling in astrocytes. Activation by 7α,25-OHC recruits β- arrestin 2 and undergoes internalization, activating MAPK and NFκB pathways to mediate inflammation. SAE-14 inhibits these effects.

classification of GPCRs has revealed relationships among receptors that are not apparent from sequence-based classifications alone, aiding in the de-orphanization process [50]. Orphan GPCRs represent a largely untapped resource for drug discovery, with significant therapeutic potential. Despite the challenges in studying these receptors due to the lack of known endogenous ligands, recent advancements in methodologies such as protein crystallography and homology modeling have facilitated the identification of potential therapeutics targeting these receptors. The increasing number of solved GPCR structures has improved the accuracy of homology models, enhancing the success rates of virtual ligand screens and experimental validation [46]. The identification of surrogate ligands through innovative approaches like the GPCR- CoIN Pocket method has also shown promise. This method identifies pharmacological similarities between GPCRs, enabling the discovery of ligands for orphan receptors based on the pharmacology of related receptors. For example, the GPCR-CoINPocket approach successfully identified surrogate ligands for the orphan receptor GPR37L1, demonstrating a 30% success rate [47]. Orphan GPCRs have been implicated in various diseases, making them attractive drug targets. For instance, GPR158 has been linked to cancer and mental illness, highlighting its potential as a therapeutic target [51]. Similarly, GPR37 and GPR37L1 have been associated with Parkinson's disease and hypertension, respectively, suggesting that targeting these receptors could lead to novel treatments for these conditions [52]. Additionally, the constitutive activity of orphan GPCRs like GPR18 in metastatic melanoma indicates their role in tumor cell survival, further underscoring their potential as anticancer targets [53].

Key Milestones

The journey into orphan GPCR research began in the late 1980s. The first notable milestone occurred in 1988 when the serotonin 5-HT1 A receptor was deorphanized by Farginet al., followed by the dopamine D2 receptor identified by Bunzowet al. These discoveries were pivotal as they employed reverse pharmacology, a method where orphan receptors are expressed in heterologous systems to identify potential ligands through binding assays [54, 55]. This approach laid the groundwork for subsequent orphan GPCR research, demonstrating that it was possible to match orphan receptors with their ligands through experimental techniques [54]. The late 1990s marked a significant increase in deorphanization efforts, coinciding with advancements in molecular biology and high-throughput screening technologies. By this time, approximately ten orphan GPCRs were being deorphanized annually, thanks to improved methodologies such as low-stringency hybridization and polymerase chain reaction (PCR)-based techniques [54, 55]. The PCR approach became particularly favored for its rapidity in identifying novel orphan GPCRs, allowing researchers to explore a wider array of potential ligands [56]. A major milestone in GPCR research was achieved in 2000 with the publication of the structure of bovine rhodops in, the first GPCR structure are solved. This was followed by the resolution of the human β2-adrenergic receptor in 2007, which provided critical insights into GPCR architecture and function [54]. These structural breakthroughs facilitated a deeper understanding of ligand-receptor interactions and opened new avenues for drug design targeting orphan GPCRs [57]. In recent years, advanced techniques such as single-cell RNA sequencing have been utilized to further elucidate the roles of orphan GPCRs in various physiological contexts. For instance, GPR87 has been identified as a biomarker in idiopathic pulmonary fibrosis, showcasing its relevance in disease pathology [54]. Additionally, novel neuropeptides such as orexin and prolactin-releasing peptide were discovered as ligands for orphan GPCRs during this period, highlighting the ongoing efforts to uncover new signaling pathways associated with these receptors [57, 58].

Table3: Phase II, III and phase IV (new agent) active and (not yet) recruiting clinical trials targeting neural cell GPCR function in different neurological disorders [110].

Target	*Disease/indication*	*Agent clinical trial phase*	*ID number for a clinical trial (Clinical Trials.gov)*
$GABA_B$ receptors	Charcot–Marie– tooth disease type 1A	Baclofen($GABA_B$ receptor agonist) Phase III+	IDNCT04762758
5-Hydroxytriptamine	Major depressive disorder with insomnia	Mirtazapine(5-$HT_2$and 5-HT_3receptor antagonist) [bPhase] IV	IDNCT05978219
(5-HT) receptors	Bipolar disorder Migraine	Lurasidone(5- HT_{2A}and5-HT_7 receptor antagonist) [cPhase] III Triptans (5-$HT_{1B}$and 5- HT_{1D}receptor agonist) Phase III	IDNCT02731612 IDNCT04946734
Dopamine receptors Adenosine receptors	Tourette's syndrome	Ecopipam($D_1$and$_5$receptor antagonist) Phase III	ID NCT0602152 2ID NCT0561522 0
	Tic disorder	Aripiprazole(partial D_2receptor agonist) [dPhase] IV	IDNCT05361993
	Diffuse pontine and midline glioma	ONC201(D_2 and D_3receptor antagonist) Phase II	IDNCT05009992
	Depression, dementia,mild cognitive impairment	Aripiprazole(partial D_2receptor agonist) [dPhase] IV	IDNCT05531591
	Migraine disorders	Metoclopramide(D_2receptor antagonist) Phase III	IDNCT05102591
	Parkinson's disease with cognitive impairment	Istradefylline(A_{2A}receptor antagonist) Phase II	IDNCT05333549
	Spinal cord injury	Istradefylline(A_{2A}receptor antagonist) Phase I/II	IDNCT05217498
	Working memory deficits	Caffeine(A_1, A_{2A}, A_{2B}, and A_3 receptor antagonist) Phase II/III	IDNCT05170464
	Postoperative, cognitive dysfunction, mild cognitive impairment	Caffeine(A_1, A_{2A}, A_{2B}, and A_3 receptor antagonist) Phase II	IDNCT05574400
	Cognition in Alzheimer's disease	Caffeine(A_1, A_{2A}, A_{2B}, and A_3receptor antagonist) Phase III	IDNCT04570085
Opioid receptors	Major depressive disorder	Aticapran (κ- receptor antagonist) Phase III Opioids (opioid receptor agonists)	IDNCT05455684
	Sleep disorder	Phase II	IDNCT04299490
	Charcot–Marie– tooth disease type	Naltrexone (opioid receptor agonist)	IDNCT04762758
		Phase III	
Melatonin receptors	Ischemic stroke, acute sleep disorders,	Melatonin (melatonin receptor agonist)	IDNCT05247125
	Circadian rhythm	Phase IV	
	Acute ischemic stroke, depression	Agomelatine(MT_1 and MT_2 receptor antagonist) Phase IV	IDNCT05426304

The exploration of orphan GPCRs continues to hold promise for therapeutic development. With over 120 orphan GPCRs remaining without identified ligands, there is significant potential for discovering new drug targets that could address unmet medical needs. The pharmaceutical industry has increasingly recognized the importance of these receptors, leading to focused efforts on deorphanization and characterization to unlock their therapeutic potential [58].

Advance Sin unveiling Orphan GPCRs

X-Ray Crystallography

X-ray crystallography plays a crucial role in elucidating the structural features of orphan GPCRs, which are essential for understanding their function. The initial challenges in crystallizing GPCRs stemmed from their low expression levels and conformational flexibility, complicating high-resolution diffraction studies. However, significant advancements have

been made in the field, including the engineering of GPCRs with fusion proteins, antibody fragment crystallization, and thermostabilizing mutations [69]. These innovations have led to the successful resolution of numerous GPCR structures, including both agonist- and antagonist-bound forms [70]. Despite these advancements, crystallizing orphan GPCRs remains challenging due to their often-unknown ligands and functional states. The first complete X-ray crystallographic structure of a GPCR was that of bovine rhodopsin in 2000, which paved the way for over 180 GPCR structures now available in the Protein Data Bank (PDB) [71]. As structural studies continue to evolve, they provide critical insights into the activation mechanisms and ligand-binding properties of orphan GPCRs [72].

History of Orphan GPCRs

Cryo-EM

Cryo-electron microscopy (cryo-EM) has revolutionized the structural analysis of orphan GPCRs, providing detailed insights into their architecture and activation mechanisms. [79]. Recent advancements have enabled the resolution of high-quality structures of various GPCRs, including orphan receptors like GPR21 and GPR179, which have been shown to adopt unique conformations that facilitate their functional roles [80, 81]. For example, the cryo- EM structure of GPR21 revealed an agonist-like motif in extracellular loop 2 (ECL2) that occupies the orthosteric pocket, promoting receptor activation even in the absence of known ligands [82]. Such structural insights are critical for understanding how orphan GPCRs function and interact with downstream signaling partners. Cryo-EM plays a pivotal role in identifying ligands for orphan GPCRs through structure-based drug design approaches. By elucidating the three-dimensional structure of these receptors, researchers can identify potential binding sites for ligands and optimize drug candidates accordingly [83].

When comparing cryo-EM with other structural biology techniques such as X-ray crystallography and nuclear magnetic resonance (NMR), each method has its strengths and limitations. Cryo-EM provides high-resolution structural data while allowing researchers to study proteins in near-native conditions without crystallization [79].The ability of cryo-EM to visualize dynamic conformational changes makes it particularly advantageous for studying orphan GPCRs,Which often exhibit significant flexibility in their structures [79].Insights gained from cryo-EM significantly influence drug development strategies for orphan GPCRs. By providing detailed structural information about receptor-ligand interactions and activation mechanisms, researchers can design more effective drugs that specifically target these receptors [81].

The future of research involving cryo-EM and orphan GPCRs looks promising as technological advancements continue to emerge. Improvements in cryo-EM resolution and sample preparation techniques will enhance our ability to study these complex receptors in greater detail [79]. Additionally, integrating computational methods such as molecular dynamics simulations with cryo-EM data could provide deeper insights into receptor dynamics and ligand interactions. As researchers continue to explore orphan GPCRs using cryo-EM, there is significant potential for discovering new therapeutic targets and developing innovative drugs that address unmet medical needs across various disease states [83]

SBDD

Structure-based drug design (SBDD)is a powerful approach that significantly enhances our understanding of the structural features of orphan GPCRs.By leveraging the three- dimensional structures of GPCRs, researchers can gain insights into their conformational states and functional mechanisms. Recent advancements in structural biology, particularly the resolution of GPCR crystal structures and cryo-electron microscopy (cryo-EM) data, have provided templates for homology modeling of orphan receptors [84]. For example, the structural elucidation of GPR88 has been pivotal in understanding its role in neuropsychiatric disorders, demonstrating how SBDD can facilitate the identification of potential therapeutic targets [85]. The availability of these structures allows for detailed analysis of ligand-binding sites and receptor dynamics, which is essential for developing effective drugs targeting orphan GPCRs [86].

SBDD plays a crucial role in identifying ligands for orphan GPCRs by enabling researchers to design small molecules that can selectively modulate receptor activity. This approach involves using structural information to predict how different ligands

Interact with the receptor, thus facilitating the identification of potential drug candidates [84]. Successful examples include the identification of novel ligands for orphan receptors through molecular docking studies, where known ligand structures are computationally screened against orphan GPCR models to find suitable candidates [86]. For instance, studies have shown that SBDD has led to the discovery of surrogate ligands for receptors like GPR97 and MRGPRX2, enhancing our understanding of their pharmacological profiles [84].

When comparing SBDD with other ligand discovery techniques such as traditional reverse pharmacology and high-throughput screening (HTS), several distinctions emerge. Traditional reverse pharmacology typically involves expressing orphan GPCRs in cell systems and screening large libraries of compounds for activity, which can be time-consuming and less efficient due to low success rates [84]. In contrast, SBDD allows for a more targeted approach by utilizing structural information to guide ligand selection and optimization. While HTS can identify active compounds quickly, it often lacks the specificity that SBDD offers through detailed structural insights into receptor-ligand interactions [87]. Consequently, SBDD is increasingly

recognized as a complementary strategy that enhances the efficiency and effectiveness of ligand discovery efforts for orphan GPCRs [88].

The insights gained from SBDD have profound implications for drug development strategies targeting orphan GPCRs. By elucidating receptor structures and understanding how ligands bind and activate these receptors, researchers can design drugs that are more selective and effective. This targeted approach minimizes off-target effects commonly associated with non-selective drugs [86]. Moreover, SBDD facilitates personalized medicine by allowing researchers to tailor drug designs based on specific receptor variants present in different patient populations [85]. As more orphan GPCR structures are resolved, the potential for developing novel therapeutics that address unmet medical needs continues to grow [84].

Future research involving SBDD and orphan GPCRs is poised for significant advancements due to ongoing developments in technology and computational methods. Enhanced computational tools for molecular docking and dynamics simulations will improve the accuracy of predictions regarding ligand-receptor interactions [86]. Additionally, integrating artificial intelligence and machine learning into SBDD workflows could accelerate the identification of promising drug candidates. As researchers continue to explore orphan GPCRs using SBDD, there is substantial potential for discovering new therapeutic targets and developing innovative drugs that address complex diseases with limited treatment options [88].

Ligand-Based Approaches

Ligand-based approaches are critical in identifying ligands for orphan GPCRs, employing various techniques to explore receptor-ligand interactions. Traditional methods such as reverse pharmacology involve expressing orphan GPCRs in cell systems and screening large libraries of compounds for activity. This approach has historically been successful but has faced challenges due to low success rates in deorphanization [89]. Recent advancements have introduced newer techniques like virtual ligand screening (VLS), which utilizes computational methods to predict how small molecules interact with orphan GPCRs based on known ligand structures. VLS allows researchers to rapidly evaluate thousands of compounds against receptor models, significantly accelerating the discovery process [90]. This combination of traditional and modern methods enhances the identification of potential ligands for orphan GPCRs [92].

Therapeutic Potential

Potential of Orphan GPCRs in Treating Diseases

Novel Drug Targets

Orphan GPCRs represent a significant opportunity as novel drug targets due to their unique roles in various physiological processes and the fact that many remain unexplored. Approximately 30% of non-olfactory human GPCRs are classified as orphan receptors, meaning they lack identified endogenous ligands [59]. This creates avenues for drug discovery that can target these receptors, potentially leading to the development of new therapeutics for conditions that currently have limited treatment options. The reverse pharmacology approach has been instrumental in identifying ligands for these orphan GPCRs, facilitating their characterizations viable drug targets [60, 64].

Diverse Disease Applications

Orphan GPCRs are implicated in a variety of diseases, including metabolic disorders, neurodegenerative diseases, and cancers. For instance, GPR35 has been linked to inflammatory responses and metabolic regulation, while GPR3 and GPR6 have shown potential roles in neurodegenerative diseases such as Alzheimer's and Parkinson's [61, 62]. Their involvement in these diseases highlights the potential for orphan GPCRs to serve as therapeutic targets across diverse medical fields, addressing unmet clinical needs [63].

Personalized Medicine

The exploration of orphan GPCRs can significantly contribute to personalized medicine approaches. By understanding the specific receptor profiles of individual patients, therapies can be tailored to target specific orphan GPCRs that may be over expressed or mutated in certain populations. This patient-specific approach could enhance treatment efficacy and minimize adverse effects, making it a promising avenue for future research [60, 62].

Biomarker Development

Orphan GPCRs also hold promise in biomarker development for disease diagnosis and prognosis. For example, GPR87 has been identified as a potential biomarker for idiopathic pulmonary fibrosis, indicating its relevance in respiratory diseases [60]. The ability to identify specific orphan GPCRs associated with particular disease states can **Aidin** early diagnosis and monitoring disease progression, ultimately improving patient management strategies [61, 64]

Improved Drug Selectivity

Targeting orphan GPCRs may lead to improved drug selectivity compared to traditional pharmacological targets. Many currently marketed drugs act on only a small subset of GPCRs, leaving a vast majority unexplored. By focusing on orphan GPCRs, researchers can develop drugs that are more selective for specific receptors, potentially reducing off-target effects and enhancing therapeutic outcomes [59]. This selectivity is particularly important in complex diseases where polypharmacy is common and side effects from non-selective drugs can significantly impact patient quality of life [63].

Combination Therapies

Orphan GPCRs can be integrated into combination

therapies to enhance treatment efficacy, particularly for chronic diseases such as diabetes and neuro degenerative disorders. For instance, GPR146 has been identified as a receptor for proinsulin C- peptide, which may help mitigate diabetes-associated complications. Current GPCR- targeting therapies, including glucagon-like peptide-1 (GLP-1) agonists and serotonin agonists, have shown promise when used in combination with standard diabetes medications, enhancing efficacy while potentially reducing side effects associated with mono therapy [66].

Understanding Disease Mechanisms

Orphan GPCRs contribute significantly to our understanding of disease mechanisms, especially in complex conditions like Alzheimer's disease, Parkinson's disease, and metabolic disorders. Research indicates that these receptors play critical roles in regulating cellular processes such as synaptic transmission and neuro inflammation. Investigating these mechanisms can lead to the identification of novel therapeutic targets and inform drug development strategies aimed at these debilitating conditions [67].

Drug Repurposing

The potential for drug repurposing to target orphan GPCRs is an emerging area of interest. Existing drugs that target known GPCRs may also interact with orphan GPCRs, providing opportunities to extend their therapeutic use. For example, certain serotonin agonists have been shown to affect orphan GPCRs, suggesting that these drugs could be repurposed for new indications related to orphan receptor activity. This strategy not only accelerates the drug development process but also offers a cost- effective approach to addressing diseases with limited treatment options [66].

Rare Disease Treatment

Orphan GPCR should promise in the treatment of rare diseases, particularly those with no established therapies. Many orphan receptors remain unexplored regarding their physiological functions and potential roles in rare conditions. For instance, GPR87 has been identified as a biomarker in idiopathic pulmonary fibrosis, indicat ing its relevance in respiratory diseases. Targeting these receptors could lead to novel treatments for are diseases by leveraging their unique signaling pathways and biological functions [69].

Modulation of Physiological Processes

Orphan GPCRs are integral to modulating various physiological processes, which has significant implications for developing novel therapeutic strategies. These receptor scan influence intra cellular signaling still about 120 GPCRs have not yet been identified as endogenous ligands. These so-called orphan GPCRs represent an unexplored area of GPCR drug discovery [65, 68].

Future Perspective

Future advances in structural biology, AI, allosteric modulation, and biased signaling will accelerate orphan GPCR drug discovery and enable the development of more selective, effective, and personalized therapies for unmet medical conditions.

Conclusion

G protein-coupled receptors (GPCRs) are a diverse family of membrane proteins essential for cellular signaling and communication, playing critical roles in various physiological processes. As significant drug targets, a large percentage of marketed pharmaceuticals act on GPCRs, underscoring their importance in drug development. This overview highlights the role of GPCRs in pharmacology, focusing on structural insights gained from advanced techniques, the challenges and opportunities presented by orphan GPCRs, and emerging trends shaping future research. GPCRs mediate responses to stimuli like hormones and neurotransmitters, influencing numerous physiological pathways. Their broad impact makes them attractive targets for therapeutic intervention in conditions such as cardiovascular diseases, metabolic disorders, neurodegenerative diseases, psychiatric illnesses, and cancer. The substantial portion of top-selling pharmaceuticals targeting GPCRs reflects their significance in modern medicine. The success of GPCRs as drug targets is attributed to well- characterized signaling mechanisms and the availability of pharmacological agents that modulate receptor activity.

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