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UP-AND-COMING SCIENTIST

Light-Sensitive Membrane Proteins as Tools to Generate Precision Treatments

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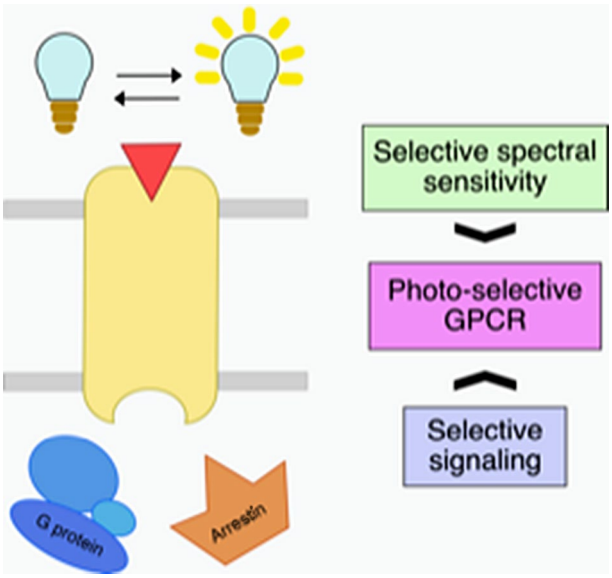
Introduction by Ana-Nicoleta Bondar, Biophysics Section Head Editor

This issue of the Journal of Membrane Biology inaugurates Up-and-Coming Scientist, in which investigators at early career stages are invited to present recent research in the broad context of their discipline. We inaugurate Up-and-Coming Scientist with the essay by Dr. Elena Lesca of the ETH Zürich and the Paul Scherrer Institut, Switzerland. Dr. Lesca has completed her doctoral degree at the Technical University München, Germany, in 2014, and pursued postdoctoral research at the ETH Zürich and Paul Scherrer Institut, where she is Senior Assistant since 2019. Two recent papers by Dr. Lesca et al. (references 33 and 39) have used X-ray crystallography and experimental biophysics approaches to shed light on the mechanism of action of a membrane receptor from the G Protein-Coupled Receptor (GPCR) family, Jumping Spider Rhodopsin-1 (JSR-1). JSR-1 is a visual rhodopsin activated upon absorption of light by its covalently bound retinal chromophore. Unlike the better-understood bovine rhodopsin GPCR, which is monostable, JSR-1 is bistable (i.e., in JSR-1 the Schiff base that binds retinal to the protein stays protonated throughout the reaction cycle), and absorption of a second photon resets the retinal ligand to the resting state configuration. In her essay, Dr. Lesca discusses the implications of her work on JSR-1 and, more broadly, GPCR research, for state-of-the-art applications in optogenetics and drug design.

Graphical Abstract



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Extended author information available on the last page of the article

A New Decade for Research to Sparkle

In 2020 the world has entered a new decade that holds a lot of promises. Medical devices will be more and more integrated with a new generation of more effective drugs and therapies. On one hand, medical and pharmaceutical companies foster new developments, and on the other hand, governments and healthcare systems seem stuck due to the high costs unsustainable in the long term (Sultana et al. 2013; European Semester for economic policy coordination: Annual Growth Survey 2017; Anderson 2016; Giordano and Schatman 2008). In this scenario, precision medicine—a patient-centric medical care—appears as an engaging solution to reduce direct and indirect costs in the future (Adjekum et al. 2017; Gavan et al. 2018). To be effective, precision medicine demands a detailed and careful investigation of the target disease: its genetics, molecular biology, and physiology. These are essential prerequisites to generate novel therapeutic approaches. Genetics, molecular and structural biology, biochemistry, biophysics, computational and system biology, and many other fields of science have joined their efforts towards a common goal: understand how molecules work, how they are regulated in a cell or tissue, how mutations affect their functionality, and so and so forth. For geneticists, single nucleotide polymorphism (SNP) may be the cause why the same drug is less effective in some patients (Petit et al. 2018; Hauser et al. 2018; Ilter et al. 2019). For biochemists, drug specificity may depend on mutations (related to the SNP) or on protein dynamics. In other words, advanced and successful therapies require a deep understanding combined with innovative technologies.

GPCRs are an Important Pharmacological Target

G protein-coupled receptors (GPCRs) are membrane proteins and influential cellular modulators involved in neurological and cardiovascular disorders, as well as in cancer and other diseases. In humans about 800 genes code for GPCRs and about 30–40% of all marked pharmaceutical drugs target GPCRs, highlighting their importance in regulating human physiology (Hauser et al. 2018; Ilter et al. 2019). All GPCRs share a similar architecture: an extracellular N terminus, seven membrane-spanning α-helices and their loops, and an intracellular C terminus. The extracellular domain contains the ligand-binding pocket (orthosteric site), while the intracellular region serves as a docking station for binding proteins (e.g., G proteins, GRKs, arrestins). Upon activation, a GPCR undergoes conformational changes from the ligand-binding pocket to the cytosolic region, triggering G protein signaling. As this is a signaling cascade, the amount of activated receptor has to be kept under control by the cell. Therefore, activated receptors are first phosphorylated by GPCR kinases (GRKs) and subsequently able to bind arrestin molecules that terminate the signaling (Gurevich and Gurevich 2019; Glukhova et al. 2018). Altogether, these multi-step signaling pathways deliver the external message to cellular components and regulate the cell and tissue physiology.

Protein X-ray crystallography and single-particle cryo-electron cryomicroscopy have disclosed the structures of several GPCRs in their inactive and active conformations (Hilger et al. 2018). These structures show the binding modes of agonist—activator—and antagonist—blocker—ligands, and they have been invaluable in the design of new drugs to modulate GPCR function. In a GPCR, the orthosteric ligand-binding site and the cytosolic-binding site communicate each other during activation through structural changes (Venkatakrishnan et al. 2019; Latorraca et al. 2017). Additionally, ligands that bind outside of the orthosteric site act as allosteric modulators (Wootten et al. 2013; Smith et al. 2018). Finally, bitopic ligands have two pharmacophores and interact with both orthosteric and allosteric sites (Ilter et al. 2019; Wootten et al. 2013).

In pharmacology, it has to be consider not only how the ligand affects the receptor funtionaly but also how it influences the signaling cascade. Indeed, the GPCR mainly acts as a transducer: it activates or stops signaling pathways influencing the cell physiology. Thus, ligands that target one signaling pathway are 'biased ligands' (Fig. 1) (Ilter et al. 2019; Hilger et al. 2018; Wootten et al. 2018). They offer higher specificity and efficacy with reduced side effects. However, the bottleneck is to understand how the binding mode of the ligand affects the conformation of the cytosolic-binding site and selects for the signaling pathway (Ilter et al. 2019; Smith et al. 2018; Wootten et al. 2018; Ehrlich et al. 2019).

Pharmacokinetics relies on in vitro measurements (Bohn et al. 2000; Sykes et al. 2019), cell-based assays (Picard et al. 2018; Ramachandran et al. 2011), knock-out mice (Ehrlich et al. 2019), and computational calculations and simulations (Sun et al. 2017). In 2018 and 2019, the large improvement of structural methods, especially single-particle cryo-electron microscopy, has allowed researchers to solve numerous structures of GPCRs in complex with G proteins and arrestin molecules (Glukhova et al. 2018; Hilger et al. 2018; Maeda et al. 2019; Zhou et al. 2016). The new abundance of data revealed that numerous factors influence the complexity of GPCR dynamics (Hilger et al. 2018; Latorraca et al. 2017; Sykes et al. 2019): receptor oligomerization and localization (Wootten et al. 2018; Pavlos and Friedman 2017; Halls 2019), intermediate states (Gurevich and Gurevich 2019; Glukhova et al. 2018; Hilger et al. 2018), receptor specificity

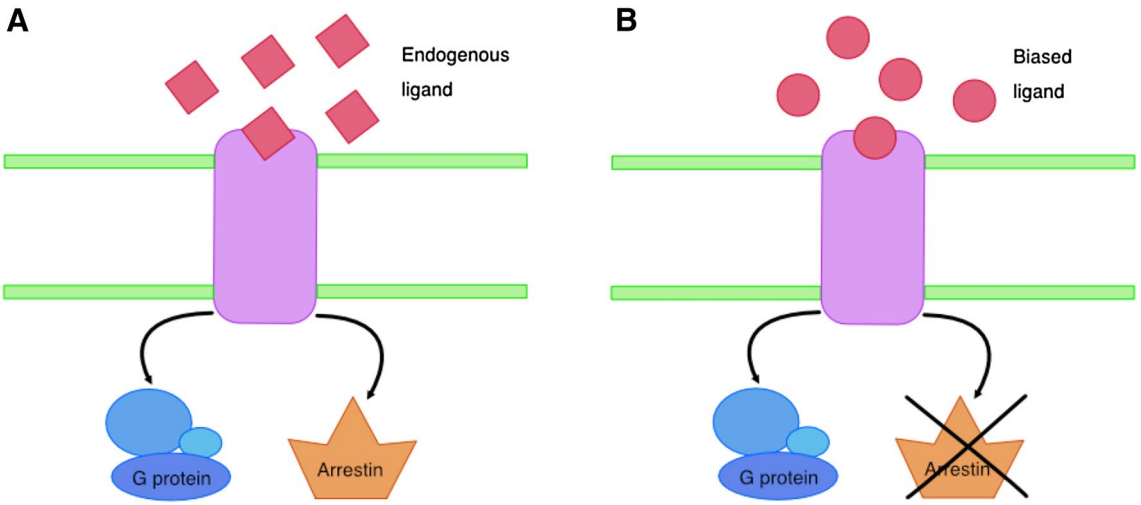

Fig. 1 Simplified difference between endogenous and biased ligands. **a** Endogenous ligands or non-selective drugs trigger receptor activation and do not distinguish which signaling pathways are further stimulated, potentially both G protein and arrestin. **b** Biased ligands are drugs that activate the receptor and selectively stimulate one signaling pathway, for instance G protein and not arrestin

for G proteins and arrestins (Gurevich and Gurevich 2019; Flock et al. 2017, 2015; Mayer et al. 2019), and internal water molecules (Venkatakrishnan et al. 2019; Angel et al. 2009; Lesca et al. 2018; Varma et al. 2019.

Light-Sensitive GPCRs as Investigation Tools

G protein-coupled receptors are important key players in neurological disorders (e.g., chronic pain, Parkinson's disease). Neurotransmitters trigger GPCR activation and, finally, intracellular signaling within a neuron and intercellular signaling amongst neurons. Neurons firing occurs within a defined spatial and temporal frame, thus reducing the efficacy and specificity of conventional pharmacological applications. In the last few years, there have been attempts to achieve light controls of proteins with an unprecedented spatial and temporal resolution to investigate synapsis in real time. Optogenetics—the use of light-sensitive proteins to control cell physiology—and photopharmacology—the use of chromophores as drugs to control proteins and cells—are growing research fields, and they have recently provided the first applicable results on GPCRs (Kleinlogel 2016; Spangler and Bruchas 2017; Bailes et al. 2012; Goudet et al. 2018).

In optogenetics, the GPCR is natively light sensitive via the covalently bound retinal chromophore (protonated Schiff base). Photon absorption causes retinal isomerization from *cis* to *trans* that, in turn, activates the receptor. There are two types of light-sensitive GPCRs. Retinal isomerization in monostable rhodopsins results in delocalization of the positive charge, which then favors the hydrolyses of the Schiff base with subsequent retinal released. In bistable opsins, the retinal remains in the ligand-binding pocket after isomerization, and it is able to accept another photon and isomerises back (Koyanagi and Terakita 1837). Understanding how the reversible isomerisation occurs would provide molecular details to exploit bistable rhodopsins as molecular switches in optogenetics. For instance, the recent data on Jumping Spider Rhodopsin-1 (JSR1) have been a turning point in the history of rhodopsin GPCRs. These are difficult proteins to study both in vitro and in vivo for numerous technical reasons. The major bottleneck is that for structural studies a large amount of proteins are required and this is usually achieved via a recombinant expression of the target. However, rhodopsins are a challenging target for recombinant expression: low yield, loss of retinal upon reconstitution, and tendency to aggregate and precipitate. Thus, bovine rhodopsin and squid rhodopsin—the two visual photoreceptors that were crystallized first—are mainly extracted from native tissue (eye retina), preventing any mutational study or application. The two publications on JSR1 provide two alternative protocols for recombinant production of the wild-type rhodopsin, as well as an extensive characterisation of its biochemical, biophysical, and structural features (Venkatakrishnan et al. 2019; Angel et al. 2009; Lesca et al. 2018). The high-resolution (2.1 Å) crystal structure of JSR1 reveals details previously unobserved in other rhodopsin structures. In JSR1 structure, the analysis of water molecules, together with biophysical and mutational studies (Ehrenberg et al. 2019; Nagata et al. 2019), allows to formulate a model of the activation mechanism in bistable rhodopsins, finally suggesting the difference with monostable rhodopsins. The work on JSR1 is an example of how the most modern pharmacological and medical approaches should root in basic research, as their success is also based on details of protein function.

Optogenetics exploits light-sensitive GPCRs: an Opto-GPCR is a fusion protein where half receptor is a rhodopsin that binds retinal, and the second half is the receptor of which the signal has to be modulated (e.g., Opto-mGluR6 and opioid receptors (Kleinlogel 2016; Spangler and Bruchas 2017)). The major limit of this approach is that rhodopsins require a laborious protein engineering to become efficient molecular switches. Monostable rhodopsins lose the chromophore upon illumination requiring a continuous source of ligand, while bistable rhodopsins reach an equilibrium after illumination preventing a full on/off switch (Ehrenberg et al. 2019; Nagata et al. 2019). Additionally, it is difficult to achieve a functional fused receptor, because the disruption and reconstruction of the transmembrane region may affect the receptor functionality (Fig. 2).

In photopharmacology, photoligands target non-photosensitive GPCRs in a reversible way (Fehrentz et al. 2011; Kienzler and Isacoff 2017). For instance, azobenzene-based switches isomerise upon illumination back and forth from a *cis* to *trans* conformation. Azobenzene derivatives have several advantages, including optimal spectral separation of the *cis* and *trans* forms, easy chemical manipulation, and derivatives with near-infrared absorption (Dong et al. 2015a, b; Beharry and Woolley 2011). Photopharmacology of GPCRs is a growing field, currently limited by ligands availability. The three major strategies of photopharmacology include diffusible photochromic ligands (PCLs) that switch between active and inactive forms; photoswitchable tethered ligands (PTLs) are covalently link to the receptor; and photoswitchable orthogonal remotely tethered ligands (PORTLs) are similar to PTLs but they use a fusion protein to interact with the target receptor (Fig. 2) (Kienzler and Isacoff 2017; Broichhagen et al. 2015). To date, a few photoswitches exist for the metabotropic glutamate receptor (Goudet et al. 2018), a class C GPCR, and there are two photoswitches for class A GPCRs: one for the Mu-opioid receptor (Schoenberger and Trauner 2014) and one for the adenosine receptor (Bahamonde et al. 2014).

Conclusion and Future Outlooks

Research on GPCR-biased signaling offers several advantages to improve precision medicine. Optogenetics and photopharmacology allow for a directional investigation of GPCR pathways with temporal resolution in vitro and in vivo. In the future, engineered light-driven GPCRs could become 'photoswitchable probes' with both spectral and protein selectivity. The unique spatial and temporal resolution of light will resolve the receptor activity in an area of a tissue or even in a subcellular area. The acquired information on GPCRs signaling from cell-based assays and in vivo experiments will also support system biology, where algorithms generate networks of receptors crosstalk for the design of new allosteric modulators.

Besides optogenetics, rhodopsin GPCRs will also address unresolved fundamental questions on GPCRs activation, as a range of light-dependent methods become accessible: from time-resolved UV–vis spectroscopy to pump-probed time-resolved serial crystallography (Ehrenberg et al. 2019; Weinert et al. 2017). For example, time-resolved serial femtosecond crystallography would provide frames of time-dependent intermediates disclosing the role of conserved water molecules in the transmembrane region, or on the ligand binding mode (Johansson et al. 2017).

Finally, there are diseases that would benefit only of a personalized cure. For instance, chronic pain may occur for a multitude of reasons and dramatically affect life conditions. Pain is a personal experience and current treatments include antidepressants and opioids, which tend to generate addiction and lose their efficacy over time. In this scenario, precision

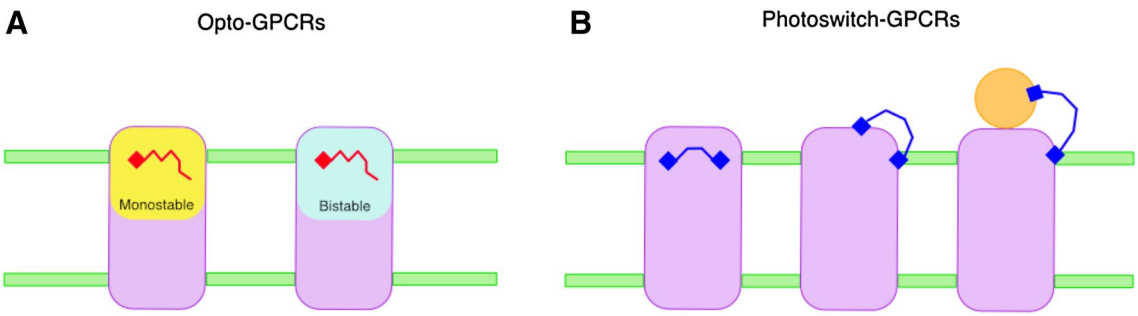

Fig. 2 Schematic overview of Opto-GPCRs and Photoswitch-GPCRs. **a** Opto-GPCRs are rhodopsins (mono- or bistable) which have been fused with the cytosolic-binding site of the receptor of interest. Monostable rhodopsins are 'one-shot' switches, and they need to be combined with a continuous supplement of retinal; bistable rhodopsins are 'on/off switches,' but they reach an equilibrium between the two states. Opto-GPCRs require extensive protein engineering to become successfully functional switches (Kleinlogel 2016). **b** Photoswitch-GPCRs exploit drugs containing a light-sensitive group. The photoswitch can interact with the GPCR mainly in three ways: directly (left), anchoring on an external residue (center), and anchoring on a binding or fusion protein (right) (Broichhagen et al. 2015; Berlin and Isacoff 2017)

medicine is a very powerful strategy. Futuristic solutions could consider biased light-activated ligands combined with an implanted electronic LED diode, which is wirelessly controlled (Mickle et al. 2019). When ON, the diode illuminates the painful area in the body, the ligand isomerises and locally interacts with target receptors, finally reducing pain. This approach would allow for a lower dose of drug and less side effects as the ligand is active only locally.

In this age of fast changes, the social and scientific communities have high expectations of research and medicine, which will soon revolutionize current treatments and, hopefully, improve life conditions.

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