Chapter 13
The Arrestin-Receptor Complex: Exciting Answers and New Questions

Yanyong Kang, Karsten Melcher, Vsevolod V. Gurevich and H. Eric Xu

Abstract To better understand the molecular mechanism of arrestin-mediated signaling, detailed structural information on the arrestin-receptor complex is necessary. Biochemical studies provided some information about how arrestins are recruited by active receptors. The X-ray laser crystal structure of the rhodopsin–arrestin complex reveals unique structural features, which include the asymmetric binding of arrestin to rhodopsin. Arrestin adopts the active conformation, with a ~20° rotation between the N- and C-domains of the molecule, which opens up a cleft in arrestin to accommodate a short helix formed by the second intracellular loop of rhodopsin. Rhodopsin–arrestin complex gives important insights into how G protein–coupled receptor signaling is terminated by arrestin and reveals structural basis of the mechanism of arrestin-biased signaling.

Keywords Crystal structure · GPCR · Rhodopsin · Arrestin · Biased signaling

Arrestins are responsible for the desensitization, internalization and G protein-independent signaling of G protein-coupled receptors (GPCRs) in an agonist-dependent manner (DeWire et al. 2007). Recent crystallographic (Kim et al. 2013; Shukla et al. 2013), mutational (reviewed in Gurevich and Gurevich 2004, 2006, 2014), and biophysical (Kim et al. 2012; Nobles et al. 2007; Zhuang et al. 2013) suggest that all arrestins undergo extensive conformational changes upon binding to the phosphorylated GPCRs. In their basal free cytosolic state, arrestins are elongated molecules, which consist of two (N- and C-) domains and the C-terminus anchored in a polar core between them, unavailable for interaction with

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partner proteins (Granzin et al. 1998; Han et al. 2001; Hirsch et al. 1999; Milano et al. 2002; Sutton et al. 2005; Zhan et al. 2011).

Crystal structure of truncated arrestin-2 (a.k.a. β-arrestin1)[1] in complex with a phosphorylated vasopressin receptor-2 (V2Rpp) carboxy-terminus revealed structural basis for arrestin activation. Activated arrestin-2 demonstrated extensive conformational changes in the C-terminus, which is released, which apparently makes it available for the interactions with clathrin (Goodman et al. 1996) and clathrin adaptor AP2 (Laporte et al. 1999). The V_2Rpp-arrestin-2 crystal structure also revealed a 20° twist between the N- and C-domains. A similar ~20° rotation has been observed in the crystal structure of pre-activated short splice variant of arrestin-1 (Kim et al. 2013), as well as the mouse visual arrestin-1 bound to a constitutively active form of human rhodopsin (Kang et al. 2015; Kim et al. 2013). It has been suggested that the twisting movement of the two domains is part of the general mechanism by which arrestins, upon activation, may expose an additional interface for interacting with their numerous binding partners. Electron microscopy analysis of β2-adrenergic receptor (β2AR) in complex with arrestin-2 (β-arrestin-1) reveals a dynamic interaction reflected in several conformations of the complex (Shukla et al. 2014).

Rhodopsin is a prototypical GPCR that serves as the photon receptor in the visual system. Along with β_2AR, rhodopsin has been a model system for studying GPCR signaling, including its coupling to downstream effectors, i.e., G proteins and arrestins. The structure of the rhodopsin–arrestin complex is the key to understanding both the receptor's conformational changes induced by arrestin binding and how different signaling pathways are activated by binding of G proteins versus arrestins (Kang et al. 2015, 2016). Here, we discuss these recent findings relating to the structural mechanism of arrestin-GPCR interaction.

Arrestin Is Asymmetrically Bound to Rhodopsin

The overall rhodopsin–arrestin structure shows that both rhodopsin and arrestin are in the active conformation (Fig. 13.1a, b). Rhodopsin and arrestin have a similar height from an intracellular view, but the width of arrestin is about three times that of rhodopsin. This arrangement allows compact crystal packing through the soluble parts of the protein complex. Arrestin consists of two β-strand domains, the N-domain and C-domain. The two domains have similar size and form a crescent molecule that interacts with the receptor (Hirsch et al. 1999). The most significant

[1]Here we use the systematic names of arrestin arrestin proteins: arrestin-1 (historic names S-antigen, 48 kDa protein, visual or rod arrestin), arrestin-2 (β-arrestin or β-arrestin1), arrestin arrestin-3 (β-arrestin2 or hTHY-ARRX), and arrestin-4 (cone or X-arrestin; for unclear reasons its gene is called "arrestin 3" in the HUGO database).

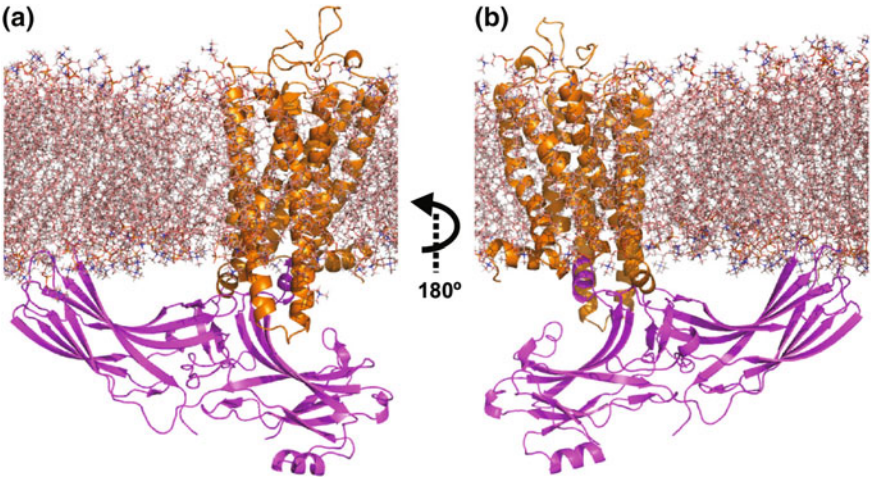

Fig. 13.1 **a**, **b** Asymmetric binding of arrestin to rhodopsin. The C-edge of arrestin likely embeds into the lipid layer through hydrophobic interactions

feature of the rhodopsin–arrestin complex is that arrestin is asymmetrically bound to rhodopsin and also asymmetrically oriented relative to the membrane (Fig. 13.1a, b). Distal tip of the C-domain contacts the cell membrane (Fig. 13.1a, b). There are many hydrophobic residues at this C-tip region, which can embed into the membrane (see Chap. 7). It is well known that other GPCR-binding proteins, the G protein heterotrimers and GPCR kinases (GRKs) need to be anchored into the membrane bilayer to perform their functions. Palmitoylation of the Gα subunit [and of GRKs 4, 5, and 6 (Gurevich et al. 2012)], and the prenylation of the Gγ subunit are involved in tethering the G proteins (or GRKs 1 and 7) to the inner surface of the plasma membrane to enable them to interact with the receptor. In contrast to GRKs and G protein subunits, there is no evidence of any lipid modification of arrestin. This asymmetric positioning of arrestin might play important role(s) in GPCR desensitization, internalization, and arrestin-mediated signaling.

The asymmetric assembly of the rhodopsin-arrestin complex was supported by three pairs of intermolecular distances between rhodopsin and arrestin measured by DEER with non-fused individual proteins (Kang et al. 2016). These results indicate that the structure of the fused rhodopsin-arrestin complex closely resembles the complex assembled by non-fused rhodopsin and arrestin. Conceivably, the asymmetric arrangement of the arrestin-rhodopsin complex might allow the distal C-tip to serve as the binding site of a second rhodopsin, which has been proposed to form dimers in the rod outer-segment disc membrane (Fotiadis et al. 2006). Although this model remains controversial (Gurevich and Gurevich 2008a, b), arrestin-1 is expressed in rod photoreceptors at the level of ~8 molecules per 10 rhodopsins

(Song et al. 2011; Strissel et al. 2006). Some experimental evidence suggests that at least at high bleach levels, when there are more light-activated rhodopsins than arrestin-1, one arrestin-1 might block two rhodopsin molecules (Sommer et al. 2011, 2014). However, high-affinity binding of arrestin-1 to monomeric rhodopsin in nanodiscs has been reported (Bayburt et al. 2011; Tsukamoto et al. 2010). Thus, the resolution of this issue awaits additional evidence.

How Arrestin Binds to Activated Rhodopsin

In comparison to the GPCR–G protein complex (Rasmussen et al. 2007), rhodopsin–arrestin complex shows a very different binding model. There are four important interfaces in the rhodopsin–arrestin complex. The first interface includes the finger loop region of arrestin and the intercellular loop 1 (ICL1), the transmembrane helix 7 (TM7), and helix 8 of rhodopsin (Fig. 13.2a). The most surprising observation is that the original finger loop region of arrestin changes its conformation to a short helix, which enables arrestin to lower the finger loop region to fit into the cleft formed by the TM bundle of rhodopsin. However, helical conformation of rhodopsin-bound finger loop of arrestin was observed in co-structure of active rhodopsin and arrestin-1 peptide (Szczepek et al. 2014). The second interface involves the middle loop and C-loop of arrestin and the ICL2 of rhodopsin. In arrestin's basal state, the middle loop and C-loop are in close proximity. When arrestin is activated, the two loops are open and provide enough space to accommodate the ICL2 of rhodopsin, which changes its conformation to a short helix (Fig. 13.2b). In the third interface, the beta strand (residues 79–86) of arrestin interacts with TM5, TM6, and ICL3 of rhodopsin (Fig. 13.2c). Because of the resolution limit of the structure, the density of the C-terminal tail of rhodopsin is not visible (Kang et al. 2015). However, based on the cysteine-cysteine crosslinking data, a computation model shows that the fourth interface involves the N-terminal β-strand of arrestin-1 and the C-terminal tail of rhodopsin (Fig. 13.2d).

Recently a number of arrestin-3 residues were implicated in receptor preference based on mutagenesis and BRET-based in-cell receptor-arrestin interaction assay (Gimenez et al. 2012b, 2014). Interestingly, the homologues of some of the C-domain residues are not even close to rhodopsin in the arrestin-1-rhodopsin structure (Kang et al. 2015). This suggests that either the pose of the non-visual arrestins bound to their cognate GPCRs is significantly different, or that identified receptor-discriminator residues act allosterically, so that their substitutions affect other residues directly engaged by the receptor. Crystal structures of at least some of the complexes of non-visual arrestins with other GPCRs are necessary to address this isuue.

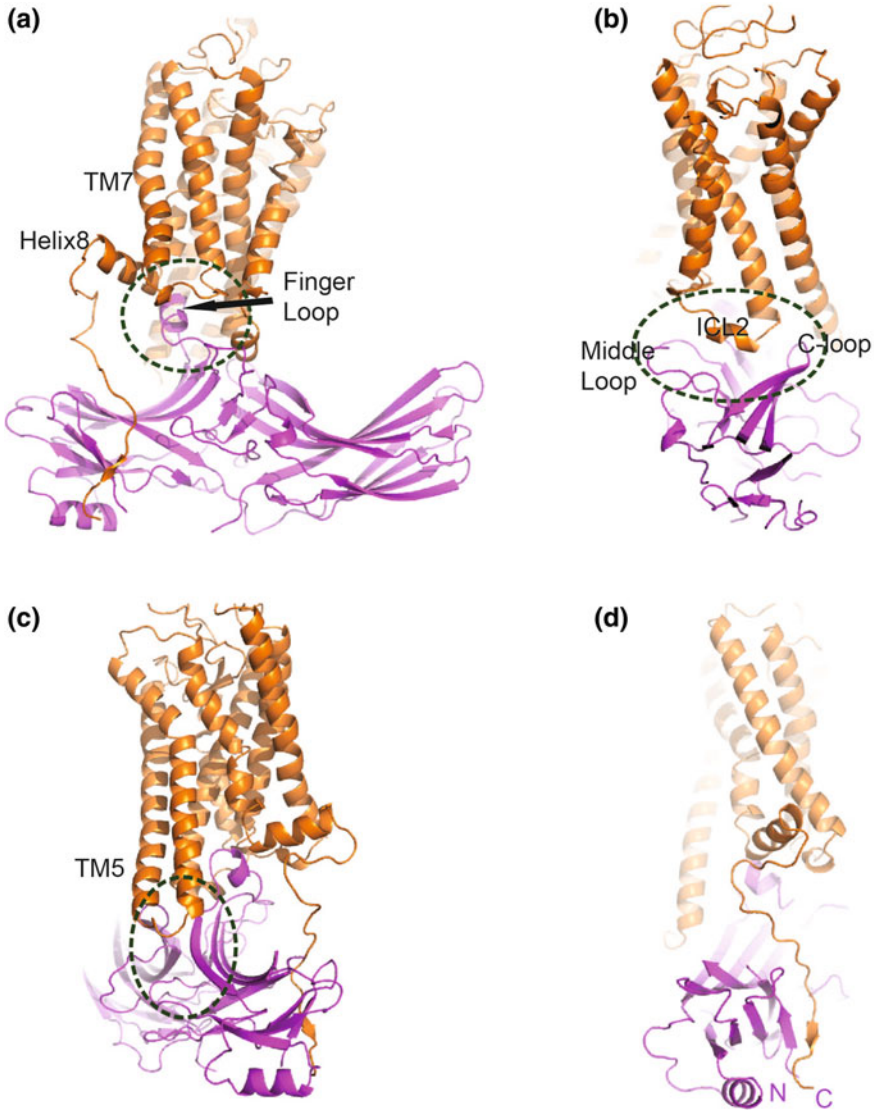

Fig. 13.2 Detailed view of the rhodopsin–arrestin interface. **a** The finger loop of arrestin-1 interacts with ICL1, TM7, and helix 8 of rhodopsin. **b** The middle and lariat loops of arrestin-1 bind to ICL2 of rhodopsin. **c** The β-strand VI of arrestin binds to TM5, TM6, and ICL3. **d** The N-C lock between the N-terminus of arrestin and the C-tail of rhodopsin

Mechanism of Arrestin Recruitment and Activation

Both G protein (Rasmussen et al. 2007) and arrestin (Kang et al. 2015) engage the inter-helical cavity that opens on the cytoplasmic side of GPCRs upon activation (Farrens et al. 1996). This explains why arrestins compete with G proteins for active GPCRs (Krupnick et al. 1997; Wilden 1995; Wilden et al. 1986). The crystal structure of the complex provides a visual model of how the GPCR is desensitized by arrestin. Compared with inactive rhodopsin, the largest difference is a 10 Å outward movement of TM6 when measured at the Cα carbon of Q244 (Standfuss et al. 2011; Zhou et al. 2012). There is also an extension of the cytoplasmic end of the TM5 helix. In addition, TM1, TM4, TM5, and TM7 show a small outward movement on the intracellular side, which creates enough space for arrestin binding. In the basal state, the two domains of arrestin are held in the basal orientation by several inter-domain interactions (Hirsch et al. 1999). When rhodopsin is activated by light, serine and threonine residues of the C-terminal tail are phosphorylated by G protein–coupled receptor kinase. The negatively charged rhodopsin C-tail displaces the arrestin C-terminus, which allows electrostatic interaction between the cationic N-terminus of arrestin and rhodopsin's C-tail, destabilizing arrestin's polar core. Once arrestin loses the polar core constraint, the N- and C-domains rotate against each other by approximately 20°, which opens up the cleft between the middle loop and the C-loop to adopt the short helix formed by the rhodopsin ICL2 (Fig. 13.2c). Because complementarily charged residues between rhodopsin and arrestin initiate the interaction, this binding is sensitive to high salt (Gurevich and Benovic 1993; Vishnivetskiy et al. 1999). There are over 800 GPCRs but only four arrestins in humans. Inspecting the charge distribution of available GPCR structures reveals a conserved pattern of positive charge on the inner side of their transmembrane helix bundle, which could form the molecular basis of promiscuous pairing between GPCRs and arrestins.

Conclusions and Future Directions

The rhodopsin–arrestin crystal structure provides the first atomic resolution view of the assembly of the rhodopsin-arrestin complex. The structure reveals an asymmetric arrangement of arrestin binding to rhodopsin and molecular basis for rhodopsin recruitment of arrestin. The intermolecular interactions and conformational changes in rhodopsin and arrestin can be used as a model for understanding other GPCR-arrestin interactions. The structural availability of both GPCR–G protein and GPCR–arrestin complexes offer an insight into different signaling pathways, which could help improve and accelerate the drug design process aiming at generating signaling-biased GPCR ligands favoring G protein- or arrestin-mediated signaling.

There remain many unanswered questions. First, what is the difference between GPCR-bound visual arrestin-1 and GPCR-bound non-visual-arrestins 2 and 3?

High-resolution crystal structures of complexes of other GPCRs with their cognate arrestins are necessary to address this question. Some GPCRs don't have long C-terminal tail, such as serotonin receptors. The serines located in the intracellular loop region can be phosphorylated (Karaki et al. 2014). The same is true for the M2 muscarinic receptor, where the third cytoplasmic loop has two clusters of phosphorylatable serines and threonines (Lee et al. 2000; Pals-Rylaarsdam et al. 1997). How are receptors phosphorylated in this element recognized by arrestin? Do they share similar binding mechanism with rhodopsin-arrestin binding? Second, what is the binding mechanism for a phosphorylated GPCR and arrestin? The structure of a pre-activated arrestin bound to a phosphorylated C-terminal tail of V2 vasopressin receptor partially addresses this question, but a complete answer still waits for a structure of arrestin in complexes with full-length phosphorylated GPCRs (Shukla et al. 2013). Interestingly, arrestin binding to some GPCRs was shown to be more dependent on receptor activation than on its phosphorylation (Gimenez et al. 2012a). New structures are needed to test an exciting hypothesis that the positions of receptor-attached phosphates create a "barcode" that determines the shape of the receptor-bound arrestin and the direction of arrestin-mediated signaling (Nobles et al. 2011; Tobin et al. 2008). Even in case of rhodopsin binding to visual arrestin-1 the role of distinct phosphorylated residues in the rhodopsin C-terminus appears to be different (Azevedo et al. 2015). Co-structures of arrestins with the same differentially phosphorylated receptor are needed to yield data shedding light on this issue. Third, what is the function of phosphoinositides in rhodopsin-mediated arrestin signaling? Phosphoinositides are the proposed physiological partners for arrestins at the plasma membrane. The crystal structure of arrestin-2 with inositol hexakisphosphate (inositol 1,2,3,4,5,6-hexakisphosphate [IP6]) has been reported (Milano et al. 2006), and IP6 is known to interact with all four arrestins, but the functional aspects are unknown. It was shown that arrestin-1 (Hanson et al. 2007, 2008a; Kim et al. 2011), as well as non-visual arrestins-2 and -3 (Chen et al. 2014; Milano et al. 2006) oligomerize, and that oligomers likely represent a storage form that does not bind receptors (Chen et al. 2014; Hanson et al. 2007). Interestingly, IP6 has opposing role in arrestin oligomerization: it promotes self-association of arrestin-2/3 (Hanson et al. 2008b; Milano et al. 2006), while inhibiting the oligomerization of visual arrestin-1 (Hanson et al. 2008b). Pursuing the answers to these questions promises to uncover important insights into biochemical mechanisms of GPCR signaling and its exploitation for biomedicine and drug discovery.

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