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β-arrestin signalling and bias in hormone-responsive GPCRs

Authors : Eric Reiter[1]*, Mohammed Akli Ayoub[1,2,3], Lucie P. Pellissier[1], Flavie Landomiel[1], Astrid Musnier[1], Aurélie Tréfier[1], Jorge Gandia[1], Francesco De Pascali[1], Shifa Tahir[1], Romain Yvinec[1], Gilles Bruneau[1], Anne Poupon[1], Pascale Crépieux[1]

Affiliation: [1] PRC, INRA, CNRS, IFCE, Université de Tours, 37380, Nouzilly, France.

[2] LE STUDIUM® Loire Valley Institute for Advanced Studies, 45000 Orléans, France.

[3] Biology Department, College of Science, United Arab Emirates University, Al Ain, United Arab Emirates.

***Corresponding author:** Eric Reiter, UMR PRC, 37380, Nouzilly, France. Telephone: +33 2 47 42 77 83; Fax: +33 2 47 42 77 43; E-mail address: Eric.Reiter@inra.fr

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Abstract

G protein-coupled receptors (GPCRs) play crucial roles in the ability of target organs to respond to hormonal cues. GPCRs' activation mechanisms have long been considered as a two-state process connecting the agonist-bound receptor to heterotrimeric G proteins. This view is now challenged as mounting evidence point to GPCRs being connected to large arrays of transduction mechanisms involving heterotrimeric G proteins as well as other players. Amongst the G protein-independent transduction mechanisms, those elicited by β-arrestins upon their recruitment to the active receptors are by far the best characterized and apply to most GPCRs. These concepts, in conjunction with remarkable advances made in the field of GPCR structural biology and biophysics, have supported the notion of ligand-selective signalling also known as pharmacological bias. Interestingly, recent reports have opened intriguing prospects to the way β-arrestins control GPCR-mediated signalling in space and time within the cells. In the present paper, we review the existing evidence linking endocrine-related GPCRs to β-arrestin recruitement, signalling, pathophysiological implications and selective activation by biased ligands and/or receptor modifications. Emerging concepts surrounding β-arrestin-mediated transduction are discussed in the light of the peculiarities of endocrine systems.

Introduction

Hydrophilic hormones bind to membrane receptors to convey signals in target cells. G protein-coupled receptors (GPCR) represent the most abundant and diversified class of membrane receptors and, as such, play major roles in endocrinology. Interestingly, GPCRs are increasingly viewed as multipurpose signal transducers which can connect to and activate multiple intracelluar pathways. GPCR-triggered intracellular signalling networks are also subjected to exquisite control of their activity in intensity, time and space. In addition to transmitting qualitative information, GPCR-mediated signalling pathways also deliver quantitative information about the strength of the stimulus. For instance, it has been reported that signalling pathways can take advantage of their nonlinear nature to convert stimulus intensity into signal duration (Behar et al., 2008). When compared to neurotransmission, which has represented the dominant paradigm in GPCR biology for decades, endocrine systems encompass much broader time scales. Indeed, some hormones are released with a pulsatile mode (Bonnefont, 2010,Gan and Quinton, 2010,Thompson and Kaiser, 2014) whereas others are characterized by long-acting actions with their levels slowly evolving in the span of days, weeks, months or even years. GPCRs' ability to traffic between different cell compartments and to transduce distinct signals as a function of their locations is also a critical facet of their function (Kholodenko et al., 2010,West and Hanyaloglu, 2015). The fact that different hormones can simultaneously hit a target cell adds yet another dimension to the complexity of endocrine systems (Noel and Kaiser, 2011).

The intricate nature of GPCR-mediated signalling was fully exemplified by the fact that β-arrestins, initially discovered for their role in the desensitization, internalization and recycling processes, were later shown to operate as signal transducer (Lefkowitz and Shenoy, 2005,Reiter and Lefkowitz, 2006). It is now clearly established that β-arrestins operate as scaffolding proteins interacting with many partners and connecting them to active GPCRs (Xiao et al., 2007). They also control the phosphorylation of a wide

array of intracellular targets (Xiao et al., 2010). Importantly, the balance between G protein and β-arrestin-dependent signal transduction at GPCRs has been demonstrated to vary from one ligand to another, strengthening the concept of ligand-directed signalling also known as pharmacological bias (Galandrin et al., 2007,Kenakin, 2003,Reiter et al., 2012). This line of thought has gained considerable momentum on the last few years as some biased compounds have been associated with reduced side-effects in the clinics (Violin et al., 2014,Whalen et al., 2011). Polymorphisms and mutations occurring at the receptor level have also been reported, in some cases, to bias signal transduction (Landomiel et al., 2014,Reiter et al., 2012,Shenoy et al., 2006,Tranchant et al., 2011,Wei et al., 2003). This review is centred on these novel ideas and how they impact our understanding of endocrine systems and the associated therapeutic approaches.

β-arrestin-mediated control of GPCR desensitization, internalization, trafficking and signalling

Over the years, the roles played by β-arrestins have continuously expanded to the point that they are now indissociably linked with all key aspects of GPCR function (**Figure 1**). The activation, desensitization and internalization of the majority of non-retinal GPCRs are critically regulated by the two non-visual arrestins: β-arrestin 1 and β-arrestin 2 (also known as arrestin 2 and arrestin 3). Two main driving forces control β-arrestin recruitment to GPCRs: agonist-induced modification of the receptor conformation and G protein-coupled receptor kinase (GRK)-mediated phosphorylation of the ligand occupied receptor (Gurevich and Benovic, 1993,Reiter et al., 2012).

The first step of receptor activation is ligand binding. The allosteric increase of a ligand's binding affinity when the receptor is complexed with its cognate G protein was conceptualized more than 35 years ago in the "ternary complex model" (De Lean et al., 1980) and was recently backed by direct structural evidences (DeVree et al., 2016). Interestingly, β-arrestin recruitment to a receptor has been reported to

induce a very similar positive allosteric effect on ligand binding, supporting the existence of an alternative ternary complex involving β-arrestins (Martini et al., 2002,Strachan et al., 2014).

β-arrestins have long been known to terminate G protein coupling (DeWire et al., 2007). Indeed, it is classically thought that the agonist-occupied active receptor is phosphorylated in its carboxyl terminus by GRK and then recruits β-arrestin with high affinity. This interaction leads to the inhibition of G protein coupling, presumably by steric hindrance (Reiter and Lefkowitz, 2006). This process generally referred to as "homologous desensitization", appears to apply to most GPCRs (Freedman and Lefkowitz, 1996). It was later demonstrated that β-arrestins also have the ability to relocate cAMP phosphodiesterases or diacylglycerol kinases to the active receptor (Nelson et al., 2007,Perry et al., 2002). This remarkable property implies that β-arrestins dually desensitize GPCRs by inhibiting G protein coupling while simultaneously enhancing the rate of second messenger degradation locally.

In addition to their role in desensitization, β-arrestins also play a central role in agonist-induced internalization of the receptor by interacting with key elements of the endocytic machinery such as clathrin (Goodman et al., 1996), clathrin adaptor AP2 (Laporte et al., 1999), small G protein ARF6 and its guanine nucleotide exchange factor, ARNO (Claing et al., 2001), and NSF (N-ethylmelaimide sensitive fusion protein) (McDonald et al., 1999). In addition, MDM2, an E3 ubiquitin ligase, binds β-arrestins and mediates their ubiquitination which is essential for clathrin-mediated endocytosis of the receptor (Shenoy et al., 2001). The presence or absence of serine and threonine clusters in the receptor carboxyl terminus regulates the affinity of β-arrestin recruitment and the pattern of intracellular trafficking of a wide number of GPCRs (Oakley et al., 2000,Oakley et al., 2001).

Beyond their roles in the control of desensitization and internalization, β-arrestins are now considered to be G protein-independent signal transducers (Lefkowitz and Shenoy, 2005,Reiter and Lefkowitz, 2006). It has been widely documented that β-arrestins are multifunctional scaffolds that interact with many

protein partners, including protein kinases, and that they impact the phosphorylation of numerous intracellular targets (Xiao et al., 2007,Xiao et al., 2010). Over the years, several approaches have been used to decipher the contributions of G proteins and β-arrestins to GPCR function. They include GRK or β-arrestin knock-outs in mice and the use of their derived MEF cell counterparts as well as selective blockade of G protein and β-arrestin pathway constituents *via* RNA silencing, dominant negative and small-molecule inhibitors. These tools have been successfully used to uncover novel signal transduction mechanisms and further characterize the pharmacology of specific GPCRs (DeWire et al., 2007,DeWire and Violin, 2011). The most thoroughly characterized signalling mechanism mediated by β-arrestins is certainly ERK1/2 MAPKs. It has been shown that β-arrestins scaffold Raf-1, MEK1, and ERK and sequester phosphorylated ERK1/2 in the cytosol (Luttrell et al., 2001). Interestingly, ERK1/2 are simultaneously activated by G protein through distinct mechanisms. G protein-dependent ERK1/2 activation is rapid and generally transient. By contrast, β-arrestin-dependent ERK1/2 activation is slower in onset but protracted. However, in some cases, G protein-mediated ERK activation can also include a sustained phase, so kinetics alone cannot always discriminate G protein- and β-arrestin-mediated ERK1/2 signalling (Luo et al., 2008). In addition, β-arrestins promote the assembly and the activation of ASK1, MKK4/7 and JNK3 (McDonald et al., 2000) as well as MKK4, MKK7and JNK1/2 (Kook et al., 2013) MAPK modules, and have been shown to trigger p38 signalling (Bruchas et al., 2006,Sun et al., 2002). The transactivation of EGF receptor by GPCRs can be regulated by β-arrestins through the activation of a transmembrane matrix metalloprotease that cleaves membrane-bound EGF ligand (Noma et al., 2007). β-arrestin 2 can inhibit NF-κB signalling through stabilization of IκBα (Gao et al., 2004). β-arrestin 1 can directly influence epigenetic modifications through nuclear interaction with histone acetylases and deacetylases that influence chromatin structure (Kang et al., 2005). Other β-arrestin-mediated signalling mechanisms include, among others, RhoA-dependent stress fiber formation (Barnes et al., 2005); protein phosphatase 2A (PP2A)-mediated dephosphorylation of Akt (Beaulieu et al., 2005); MNK-dependent

induction of protein translation (DeWire et al., 2008) and p90RSK-dependent anti-apoptotic effects (Ahn et al., 2009); phosphatidylinositol 3-kinase (PI3K)-mediated phospholipase A2 (PLA2) activation (Walters et al., 2009) and PTEN activation downstream of RhoA/ROCK (Lima-Fernandes et al., 2011).

At the molecular level, it has been shown, using different experimental approaches, that β-arrestins 1 and 2 undergo conformational changes upon interaction with phosphorylated carboxyl terminus of receptors (Charest et al., 2005,Nobles et al., 2007,Xiao et al., 2004). Early data also supported the notion that ligand-induced, functionally specific receptor conformations can be translated to specific β-arrestin conformations and impact their intracellular activities (Shukla et al., 2008). This view has recently been further explored using intracellular BRET or FRET probes capable of sensing β-arrestin conformational repertoire with better accuracy (Lee et al., 2016,Nuber et al., 2016). These studies concluded that distinct β-arrestin conformations can be stabilized in a receptor and/or ligand-specific manner.

Interestingly, different GRK subtypes have been reported to play specialized regulatory functions. Second messenger generation has been shown to be dampened by GRK2 yet unaffected by GRK5 or GRK6 whereas β-arrestin 2-dependent ERK activation required GRK5 and GRK6 action (Iwata et al., 2005,Kara et al., 2006,Kim et al., 2005,Ren et al., 2005,Shenoy et al., 2006,Zidar et al., 2009). In light of these results, it has been hypothesized that there is a GRK-induced phosphorylation “bar code” at the C terminus of GPCRs that regulates the nature of β-arrestin intracellular functions (Kim et al., 2005,Reiter and Lefkowitz, 2006,Shenoy et al., 2006,Tobin et al., 2008). Independent studies demonstrated that GPCR phosphorylation is indeed preferentially directed to specific sites in a ligand and kinase-dependent manner (Busillo et al., 2010,Butcher et al., 2011,Heitzler et al., 2012,Nobles et al., 2011,Yang et al., 2015).

Structural details of GPCR-β-arrestin interaction have recently started to emerge as crystal structure of rhodopsin-arrestin complex exhibited an engagement of the receptor core with visual arrestin (Kang et al., 2015). Importantly, visualization of β2AR-V2R–βarr1 complex by negative-stain electron microscopy

and cross-linking has directly demonstrated two interaction modes existing between GPCR-β-arrestin (Shukla et al., 2014). Indeed, in addition to β-arrestin engagement with the receptor core, these new data report the existence of a distinct interaction site between the phosphorylated carboxyl terminus of GPCRs and the N-domain of β-arrestins. Further, functionality of the receptor-β-arrestin complex formed with the phosphorylated carboxyl terminus was recently revealed (Kumari et al., 2016). The interaction of β-arrestin with the phosphorylated carboxyl terminus but not the receptor core could lead to receptor internalization, ERK MAP kinases binding to β-arrestin 1 and their subsequent activation. Furthermore, the same study revealed that the β-arrestin-biased ligand carvedilol does not induce the engagement between β-arrestin 1 and the receptor core. A recent model has been built using a docking algorithm and predicted the assembly of the ERK MAP kinase scaffold on β-arrestin (Bourquard et al., 2015). This model was compatible with β-arrestin interacting with either domain.

β-arrestin and G protein-biased signalling

A recent outburst of structural, biophysical and pharmacological evidences has profoundly transformed our vision of GPCR activation and therapeutic targeting. Not that long ago, it was thought that one inactive conformation of a receptor was in equilibrium with a single ligand-bound active conformation. Accordingly, the strength of an agonist was supposed to directly reflect the proportion of active *versus* inactive receptor conformation. The discovery of partial and inverse agonists revealed new levels of pharmacological properties beyond full agonists and neutral antagonists, but those types of activities were still consistent with the two-state model. Several examples were found that did not fit this paradigm: compounds generated different relative potencies in different assays (Watson et al., 2000). These findings, controversial at first, were repeated with a growing number of GPCRs. In the meantime, the fact that multiple active and inactive receptor conformations co-exist had been supported by

overwhelming structural and biophysical evidences (Kobilka, 2011,Nygaard et al., 2013,Wacker et al., 2013). Consequently, pharmacological theory has been revised and efficacy is now considered as being multi-dimensional and explicitly incorporate the notion that receptors engage distinct subsets of their full signaling repertoire (Galandrin et al., 2007). This means that different subsets of conformations can be stabilized by different agonists or mutation/polymorphism at a given GPCR and that each of these conformational ensembles is connected to distinct transduction mechanisms. This is the concept or pharmacological bias (Kenakin, 2003,Reiter et al., 2012,Violin and Lefkowitz, 2007). According to these principles, it is possible to selectively control pathway activation with biased ligands or specific amino-acid modifications. Orthosteric sites on GPCRs bind endogenous agonists and are also recognized by classic competitive antagonists and inverse agonists. By contrast, allosteric sites on a receptor are distinct from the orthosteric site and can affect either positively or negatively receptor activity in conjunction with orthosteric ligands or alone. Importantly, synthetic allosteric modulators for GPCRs are now being discovered at a high rate and can also lead to pharmacological bias, providing novel avenues in drug discovery (Changeux and Christopoulos, 2016). These allosteric ligands can modulate receptor conformations in the presence of orthosteric ligands and therefore have the potential to fine-tune, positively or negatively responses elicited by endogenous or synthetic ligands.

The study of pharmacological bias has rapidly become an extremely active field of research and, once again, β-arrestins hold a prominent position since large numbers of ligands displaying bias on β-arrestin-mediated functions have been reported. Certain biased ligands favour G protein-dependent transduction whereas others preferentially trigger β-arrestin-mediated pathways when compared to a reference ligand. Importantly, biased ligands capable of stabilizing a subset of the receptor conformation repertoire have been reported to improve the balance between side effects and benefits (Whalen et al., 2011). The advent of novel non-conventional classes of GPCR-targeting compounds such as pepducins (Carr and Benovic, 2016), aptamers (Kahsai et al., 2016), intrabodies (Staus et al., 2014) or nanobodies

(Mujic-Delic et al., 2014,Staus et al., 2016) extend even more the range of possibilities for innovative drug discovery approaches to be developed in the future.

So far, biased ligands have concentrated most of the attention in the field of GPCR pharmacology as they represent potential leads for the development of new drugs. However, the whole concept of bias equally applies to modifications occurring at the receptor level (Landomiel et al., 2014). The first examples of mutations leading to β-arrestin-bias have been the angiotensin type 2 receptor DRY-AAY (Wei et al., 2003) and the β2AR-TYY (Shenoy et al., 2006) mutants. This notion of pharmacological bias also plays a crucial role in medicine as it can materialize in patients through mutations or polymorphisms. Therefore, the concept of pharmacological bias changes the way to investigate the functional consequences of mutations and polymorphisms occurring at the receptor level. This type of question was traditionally assessed by tracking loss or gain of function according to the simple two-state model. Now, the exploration needs to integrate the multiple dimensions of receptor activity through multiplexed analyses of the different signalling pathways induced downstream receptor activation.

β-arrestins' roles in the control GPCR-mediated signals in time and space

One major conundrum associated with GPCR signalling resides in the fact that the numbers of ligands and receptors appears to largely overcome the relatively limited number of transduction mechanisms and downstream signalling pathways available. To circumvent this problem, it has been proposed that the signalling machinery may use spatial and temporal encoded patterns in order to maintain the full complement of information and specificity conferred by the receptor/ligand pair (Lohse and Hofmann, 2015). In this view, the signalling events triggered by a GPCR are characterized by their kinetics and spatial patterns and correspond to a signature specific of the receptor, cellular context and nature of the ligand. The regimen of exposure to the ligand may also lead to specific signalling signatures, a possibility

that could be of particular relevance in the context of endocrine systems. The kinetic and spatial aspects of GPCR signalling have only begun to be explored with the elucidation of the dynamics of receptor activation, G protein coupling and G protein activation for some receptors (Jensen et al., 2009,Lohse et al., 2008). In the classical model, G protein signalling originates at the cell surface and is followed by rapid β-arrestin-mediated quenching of G protein signalling. Recent findings have begun to challenge this paradigm. A number of GPCRs have been reported to elicit sustained G protein signalling, rather than being desensitized after initial agonist stimulation (Calebiro et al., 2009,Feinstein et al., 2013,Ferrandon et al., 2009,Irannejad et al., 2013,Mullershausen et al., 2009). For instance, it has been recently proposed that, for some GPCRs, a series of distinct signalling waves could arise upon activation (Lohse and Calebiro, 2013). In this model, a first wave is triggered at the cell surface upon G-protein coupling and results in the classical second messenger release. A second wave follows either from clathrin-coated pits and or from clathrin-coated vesicles when β-arrestin associated with the receptor induces signals such as ERK activation. A third wave which has been recently described involves signalling via G proteins from the endosomal compartment and may have specific physiologic outcomes (Calebiro et al., 2009,Calebiro et al., 2010,Feinstein et al., 2011,Feinstein et al., 2013,Ferrandon et al., 2009,Irannejad et al., 2013,Ismail et al., 2016,Mullershausen et al., 2009,Tsvetanova et al., 2015,Vilardaga et al., 2014)(**Figure 1**). These findings are in contradiction with the classical view of GPCR signalling in which persistent interaction of β-arrestin with the receptor should prevent G protein activation. X-ray crystallography of the β2AR in complex with Gαs has revealed that the interaction involves both the N-terminal and C-terminal domains of the Gαs subunit and the core of the receptor (*i.e.*: intracellular loop 2, transmembrane domain 5 (TM5), and TM6)(Rasmussen et al., 2011). As discussed above, a recent study revealed that β-arrestin interact with two different sites on the receptor; one is the phosphorylated receptor carboxyl terminus and a second, within the core of the receptor (Shukla et al., 2014). Importantly, internalized receptor complexes called “megaplexes” composed of a single GPCR, β-arrestin, and G protein were recently

discovered and their architecture and functionality described (Thomsen et al., 2016). These ''megaplexes'' seem to preferentially form with receptors that interact strongly with β-arrestins via a C-terminal tail containing clusters of serine/threonine phosphorylation sites. Single-particle electron microscopy analysis of negative-stained purified megaplexes revealed that a single receptor can simultaneously bind through its core region with G protein and through its phosphorylated carboxyl terminus with β-arrestin. The formation of such megaplexes provides a mechanistic basis for the newly appreciated sustained G protein signalling from internalized GPCRs. It is remarkable that, with only one exception, the studies on endosomal G protein signalling reported so far involve hormone-responsive GPCRs (*i.e.*: TSHR, PTHR, β2AR, V2R and GIPR). This observation suggests that receptors that are chronically exposed to their cognate hormone could take advantage of endosomal signalling to remain active despite being continuously desensitized when at the plasma membrane.

Another very interesting illustration of β-arrestins' importance in the control of signals in space, time and sensitivity recently came from a study of cAMP signalling by the RXFP1 relaxin receptor (Halls and Cooper, 2010,Halls, 2012). Relaxin is known to circulate at a very low (sub picomolar) concentration and yet is able to trigger cAMP signalling (Halls, 2012). A molecular mechanism is now provided with the constitutive assembly of a RXFP1-signalosome made of Gαs, Gβγ, adenylyl cyclase 2 (AC2) functionally coupled to AKAP79, with the latter bound to helix 8 of RXFP1. Importantly, β-arrestin 2 simultaneously associates with the carboxyl terminus of RXFP1 and scaffolds protein kinase A (PKA) and PDE4D3. In this signalosome, the activation of AC2 is thus tonically opposed by protein kinase A (PKA)-activated PDE4D3. This RXFP1-signalosome enables receptor to respond to attomolar concentration of relaxin and reveals a concentration-biased agonism as the signalosome is disrupted at nanomolar concentrations of relaxin and above (Halls and Cooper, 2010). Noticeably, other hormones -gonadotropins for instance- also activate cAMP signalling at very low circulating concentration (*i.e.*: EC_{50} in the picomolar range) which is hard to explain on the basis of receptor occupancy alone (Ayoub et al., 2015). The existence of RXFP1-

like pre-assembled signalosomes at other hormone-responsive GPCRs is therefore potentially interesting and deserves investigations in the future.

Pathophysiological implications of β-arrestin bias in endocrine systems

When assessing whether or not a receptor is functionally coupled to β-arrestins, the first step is generally to measure the ability of the former to recruit the latter. Most of the earlier studies relied on co-immunoprecipitation between the receptor and β-arrestins and/or on the visualization of β-arrestin-GFP fusion protein colocalisation with the receptor by confocal microscopy. Characteristic patterns of recruited β-arrestins-GFP were soon identified and allowed classifying receptors according to the strength of their association with β-arrestins (Oakley et al., 2000,Oakley et al., 2001). This property also facilitated the study of β-arrestin recruitment to receptors, often making co-localization with the receptor unnecessary. However, these approaches were not very sensitive and often required overexpression of both β-arrestin and receptor to high levels or, in the case of immunoprecipitation with endogenous β-arrestins, the use of a cross-linking agent. The situation dramatically improved with the advent of resonance energy transfer technologies (fluorescence resonance energy transfer [FRET] and bioluminescence energy transfer [BRET]) which are much more sensitive, quantitative and allow higher throughput. These FRET/BRET approaches generally require the receptor as well as the β-arrestin to be expressed as proteins fused to a compatible donor/acceptor pair. An intramolecular BRET sensor, capable of detecting changes in β-arrestin conformation named “double brilliance”, was later reported (Charest et al., 2005). Interestingly, this double brilliance sensor can be used with endogenously expressed native receptors as both the donor and the acceptor are attached to the β-arrestin. In parallel, very sensitive split-TEV reporter assays were developed (Barnea et al., 2008). More recently, sophisticated quantitative confocal microscopy approaches have been successfully used to study GPCR at single molecule level (Jonas et al., 2016) and track β-arrestin recruitment (Eichel et al., 2016).

Interestingly, different combinations of these approaches have been successfully applied to a large number of hormone-responsive GPCR (**Table 1**). The one notable exception is the mammalian GnRH receptor for which no β-arrestin recruitment could be measured. Interestingly, GnRH receptors from mammals are characterized by their complete lack of carboxyl terminus and their resistance to desensitization. An important proportion of the hormone-responsive GPCR were also found to be biased as a consequence of mutations/polymorphisms at the receptor level (receptor bias), activation by particular ligands (ligand bias) or a combination of both (**Table 1**). Thus, most hormone-responsive GPCRs have already been reported to recruit β-arrestins upon agonist stimulation and for the majority of them functional consequences could be linked with β-arrestins in *in vitro* settings. The next question naturally is whether this translates into physiologically or pathologically relevant situations. Literature survey revealed that β-arrestin-dependent signalling has already been associated with pathophysiological settings for eleven hormone-responsive GPCRs (**Table 2**). Some of the studies were based on genetic mutations leading to signalling bias: V_2R (diabetes insipidus and nephrogenic syndrome of inappropriate antidiuresis [NSIAD]), FSHR (fertility disorders), GPR54 (hypogonadotropic hypogonadism) and PKR2 (Kallmann syndrome). Other studies reported the effects of biased ligands: β_1AR (memory consolidation), β_2AR (heart failure, cardiomyocyte contraction), AT_1R (increased cardiac performance with reduced blood pressure), PTH_1R (osteoporosis) and GLP_1R (diabetes). Finally, some *in vivo* effects were obtained using knockout of β-arrestins in mice or in tumour cells: CCKAR, CCK1R (insulin secretion and protection of β cell mass), GPR54 (breast cancer cells invasiveness), ET_AR (epithelial ovarian cancer cell tumorigenesis). Considering the fact that the exploration of β-arrestin signalling in the context of endocrine systems, especially in *in vivo* settings, is still in its infancy, the current state of the art is very encouraging. Novel tools which will greatly facilitate assessments of β-arrestin signalling *in vivo* are developing very fast. Obviously, as discussed in this review, the whole field of biased ligands has exploded, including for endocrinology-relevant GPCRs. Exome sequencing has also come to the fore and

will undoubtedly uncover novel genetic mutations and polymorphisms, some of them potentially leading to bias. More sophisticated genetically-modified mouse models, allowing for instance conditional knockouts of β-arrestins should be available soon. Therefore, there is little doubt that β-arrestins are going to be associated with more and more pathophysiological situations in endocrine systems. The molecular characterisation of these effects should also reach an unprecedented level of detail and sophistication.

Conclusions

Over the last 15 years, β-arrestins have evolved from proteins specialized in the desensitization and internalization of GPCRs to the status of major players affecting all the facets of GPCRs signalling. In the meantime, the interest in the endocrinology field for β-arrestins has considerably grown, to reach a point where most hormone-responsive GPCR classes have been investigated, at minimum for their ability to recruit them and signal through them. Obviously, the elucidation of β-arrestin-dependent mechanisms which are specifically associated with hormone-responsive GPCRs still has ways to go. But the challenge is exciting because the study of endocrine systems may uncover novel aspects of β-arrestin functions, and also because deciphering β-arrestin-dependent mechanisms will undoubtedly lead to a better understanding of endocrinology at cellular and molecular levels. The technological toolbox as well as the conceptual framework available to explore β-arrestin functions have also dramatically improved, making sophisticated dissection of signalling mechanisms as well as pharmacological profiling more tractable than before. Clear physiological and pathological implications of β-arrestins in endocrinology have already been established for several hormone/receptor pairs. Last but not least, the close connection between β-arrestin signalling and biased pharmacology open novel and promising avenues in drug discovery, with some hormone-responsive GPCR already being at the centre of attention from

pharmaceutical industry. It can be foreseen that a virtuous cycle will form, with these drug discovery programs delivering basic scientists with invaluable research tools that will in turn help push the concepts further.

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Hormone	Class A Receptor	Methodology	Receptor bias	Ligand bias	References
Cholecystokinin	CCKAR, CCK1R	Microscopy		β-arr-independent internalization	(Cawston et al., 2012,Ning et al., 2015)
Gastrin	CCKBR, CCK2R	Microscopy; BRET	Reduced β-arr affinity (S/T in C-term; M134A; Y380A)	G protein bias	(Barak et al., 2003,Magnan et al., 2011,Magnan et al., 2013)
Neuropeptide Y	NPY1R, NPY2R	Microscopy; BRET; BiFC; FCS	Reduced β-arr affinity at NPY1R: truncation/substitutions in C-term; increased β-arr affinity at NPY2R: H155P	Bias towards or against β-arr-dependent internalization	(Berglund et al., 2003,Gimenez et al., 2014,Holliday et al., 2005,Kilpatrick et al., 2012,Made et al., 2014,Ouedraogo et al., 2008)
Pancreatic polypeptide	PPYR1, NPY4R, NPY5R	Microscopy; BRET		Bias towards or against β-arr-dependent internalization	(Berglund et al., 2003,Made et al., 2014)
Vasopressin	$V_{1A}R$, $V_{1B}R$, V_2R	Microscopy; BRET; split-TEV; LRET; luminescence emission decay	Constitutive β-arr recruitment and internalization (R137H); increased Gs and β-arr recruitment (R137C, R137L); Gs-bias (R181C, N181C); Constitutive Gs activation with no β-arr recruitment (I130N)	β-arr bias; Gs-bias	(Barak et al., 2001,Coulon et al., 2008,Djannatian et al., 2011,Erdelyi et al., 2014,Erdelyi et al., 2015,Jean-Alphonse et al., 2009,Kashiwazaki et al., 2015,Khoury et al., 2014,Martini et al., 2002,Oakley et al., 2000,Rahmeh et al., 2012,Tenenbaum et al., 2009,Terrillon et al., 2003,Terrillon et al., 2004)
Oxytocin	OXTR	Microscopy; BRET	Reduced β-arr affinity and internalization: S/T in C-term	Gi1/Gi3 bias; β-arr bias; Gq bias	(Azzi et al., 2003,Busnelli et al., 2012,Busnelli et al., 2013,Di Benedetto et al., 2014,Hasbi et al., 2004,Oakley et al., 2001,Passoni et al., 2016,Terrillon and Bar-Sagi, 2008)
Adrenaline, epinephrine	α_1AR, α_2AR, β_1AR, β_2AR, β_3AR	Microscopy, co_IP; split-TEV	β-arr bias (T68F,Y132G,Y219A)	Gs biased ligands and pepducins; β-arr bias	(Drake et al., 2008,Littmann et al., 2015,Oakley et al., 2000,Shenoy et al., 2006,Small et al., 2006,Stanasila et al., 2008,Wisler et al., 2007)
Gonadotropins	FSHR, LHR	Microscopy; co-IP; BRET	Reduced β-arr affinity: S/T in C-term; β-arr bias (A189V)	Diverse G and β-arr bias	(Ayoub et al., 2015,Ayoub et al., 2016,Casarini et al., 2016,Kara et al., 2006,Tranchant et al., 2011,Wehbi et al., 2010,Wehbi et al., 2010)
TSH	TSHR	Microscopy			(Frenzel et al., 2006)
TRH	TRHR	Microscopy; co-IP; BRET	Impaired β-arr recruitment and internalization (Δ C-term)		(Groarke et al., 2001,Hanyaloglu et al., 2002,Jones and Hinkle, 2008,Kocan et al., 2008,Oakley et al., 2000,Scott et al., 2002)
Melatonin	MT1R, MT2R	BRET; FRET; co-IP; split-TEV	Bias towards the ERK (MT1-G166E, MT1-I212T); bias towards cAMP (MT2-V124I)		(Bondi et al., 2008,Cheng et al., 2006,Hong et al., 2016,Kamal et al., 2009,Sakurai et al., 2014,Sethi et al., 2010)
Angiotensin	AT_1R,	Microscopy; co-IP; BRET; double brilliance β-arr	β-arr-bias (DRY-AAY, D74N)	β-arr-bias	(Ahn et al., 2004,Cabana et al., 2015,DeWire and Violin, 2011,Lee et al., 2016,Namkung et al., 2016,Porrello et al., 2011,Rakesh et al., 2010,Santos et al., 2015,Sauliere et al., 2012,Tang et al., 2014,Valero et al., 2016,Violin et al., 2010,Wei et al., 2003)
Kisspeptin	GPR54	Microscopy; co-IP	β-arr-biased ERK activation (L148S)		(Ahow et al., 2014,Goertzen et al., 2016,Harms et al., 2003,Millar and Babwah, 2015,Navenot et al., 2009,Pampillo et al., 2009,Szereszewski et al., 2010,Zajac et al., 2011)
Orexin	OX_1R, OX_2R	Microscopy; co-IP; BRET			(Dalrymple et al., 2011,Jaeger et al., 2014,Milasta et al., 2005,Navarro et al., 2015,Robinson and McDonald, 2015)
Somatostatin	SST_2R, SST_3R, SST_5R	Microscopy; co-IP; BRET		β-arr and G protein bias	(Grant et al., 2008,Lehmann et al., 2016,Lesche et al., 2009,Liu et al., 2005,Peverelli et al., 2008,Poll et al., 2010,Tulipano et al., 2004,Zhao et al., 2013)

Melano-cortin	MC_1R, MC_2R, MC_3R, MC_4R, MC_5R	Microscopy; BRET; co-IP; split-TEV; cell fractionation	Constitutive β-arr recruitment (E92K); decreased internalization (T312A, S329A/S330A)		(Abrisqueta et al., 2013,Benned-Jensen et al., 2011,Breit et al., 2006,Cai et al., 2004,Kilianova et al., 2006,Nyan et al., 2008,Rodrigues et al., 2012,Roy et al., 2011,Shinyama et al., 2003)
Tachykinin	NK_1R, NK_2R, NK_3R	Microscopy; BRET; FRET; co-IP; cell fractionation	Impaired β-arr recruitment, internalization and ERK activation (NK1RΔ325); G protein and β-arr-biased mutants		(Cézanne et al., 2004,DeFea et al., 2000,Grasso et al., 2013,Jafri et al., 2006,Martini et al., 2002,McConalogue et al., 1998,Pal et al., 2013,Poole et al., 2015,Richardson et al., 2003,Schmidlin et al., 2002,Schmidlin et al., 2003,Yamaguchi et al., 2016,Zimmer et al., 2003)
Prokineticin	PKR1, PKR2	Microscopy; BRET, dominant negative	β-arr-bias (R85C, R85H, R164Q, V331M); G protein-bias (R80S) No coupling to Gi/o (R268C)		(Sbai et al., 2014,Yin et al., 2014)
Ghrelin	GhrelinR (GHSR1a)	Microscopy; BRET	G protein-bias (P148A) β-arr-bias (L149G)		(Chebani et al., 2016,Lodeiro et al., 2009)
Endothelin	ET_AR, ET_BR	Split-TEV; siRNA-mediated depletion		G protein bias	(Cianfrocca et al., 2010,Maguire et al., 2012)
Apelin	ApelinR	Microscopy; BRET	G protein bias (Ser348)	Gi bias (Apelin-K16P)	(Ceraudo et al., 2014,Chen et al., 2014,Lee et al., 2010)
Prostanoids	DP_1R, DP_2R, EP_1R, EP_2R, EP_3R, EP_4R, FPR, IPR, TPR	Microscopy; BRET; split-TEV	Impaired β-arr recruitment	G protein and β-arr bias	(Erdelyi et al., 2015,Gallant et al., 2007,Jiang and Dingledine, 2013,Leduc et al., 2009,Reid and Kinsella, 2007,Rochdi and Parent, 2003)
Motilin	MotilinR	Microscopy			(Mitselos et al., 2008)
Relaxin	$RXFP_1R$, $RXFP_2R$, $RXFP_3R$	Microscopy; BRET; co-IP		G protein bias; dose-dependent bias	(Halls and Cooper, 2010,Halls, 2012,Kocan et al., 2014)
Leukotriene	BLT_1R, BLT_2R, $CysLT_1R$, $CysLT_2R$, OXER, FPR_2/ALXR	Microscopy; FRET; BRET; slit-TEV		β-arr bias	(Foster et al., 2013,Jala et al., 2005,Jala and Haribabu, 2010,Konya et al., 2014,Yan et al., 2011)
Hormone	**Class B Receptor**	**Methodology**	**Receptor bias**	**Ligand bias**	**References**
VIP, PACAP	$VPAC_1R$, $VPAC_2R$, PAC_1R	Microscopy; co-IP; siRNA-mediated depletion and KO MEFs			(Broca et al., 2009,Shetzline et al., 2002)
Corticotropin-releasing factor	CRF_1R, CRF_2R	Microscopy; co-IP; BRET; FRET; siRNA-mediated depletion; KO MEFs	Impaired β-arr recruitment (truncation or Ser/Thr mutation in ICL3 and C-term		(Bangasser et al., 2010,Bonfiglio et al., 2013,Dunn et al., 2016,Hauger et al., 2013,Holmes et al., 2006,Markovic et al., 2008,Milan-Lobo et al., 2009,Navarro et al., 2015,Oakley et al., 2007,Rasmussen et al., 2004,Teli et al., 2005)
PTH	PTH_1R, PTH_2R	Microscopy; co-IP; siRNA-mediated depletion; KO mice; FRET	Impaired β-arr recruitment (truncation of C-term; Ser/Thr mutation C-term; N289A; K382A)	β-arr bias	(Bianchi and Ferrari, 2009,Feinstein et al., 2011,Ferrari et al., 2005,Gesty-Palmer et al., 2006,Gesty-Palmer et al., 2009,Vilardaga et al., 2001,Vilardaga et al., 2002,Wehbi et al., 2013)
Glucagon, GLP1, GLP2, GIP, Secretin	GHRHR, GIPR, GLP_1R, GLP_2R, SCTR	Co-IP; split-TEV; BRET; FRET; siRNA-mediated depletion		G protein and β-arr-bias Biased cooperativity	(Al-Sabah et al., 2014,Jorgensen et al., 2005,Jorgensen et al., 2007,Quoyer et al., 2010,Sonoda et al., 2008,Talbot et al., 2012,Wootten et al., 2013,Wootten et al., 2016,Zhang et al., 2015)
Calcitonin	AMY_1R, AMY_2R, AMY_3R, CGRPR, AM_1R, AM_2R, CTR, CALRLR	Microscopy; BRET; β-arr dominant negative		β-arr bias	(Hay et al., 2014,Héroux et al., 2007,Hilairet et al., 2001,Padilla et al., 2007)

Table 1: β-arrestin recruitment and bias associated with hormone GPCRs.

Hormone	Receptor	Pathophysiological implications of β-arrestin-dependent signalling	References
Cholecystokinin	CCKAR, CCK1R	β-arr1 is a key mediator of CCK-mediated insulin secretion and of its protective effect against apoptosis in pancreatic beta cells.	(Ning et al., 2015)
Vasopressin	V_2R	Mutations introducing G protein or β-arrestin bias at V_2R in familial nephrogenic diabetes insipidus and in nephrogenic syndrome of inappropriate antidiuresis (NSIAD)	(Barak et al., 2001,Erdelyi et al., 2015,Jean-Alphonse et al., 2009,Tenenbaum et al., 2009)
Adrenaline epinephrine	β_1AR β_2AR	β-arr-biased signalling at β_1AR mediates memory reconsolidation; carvedilol is a β-arr-biased agonist with proven efficacy in the treatment of heart failure; carvedilol and a β-arr-biased pepducin promote cardiomyocyte contraction	(Carr et al., 2016,Liu et al., 2015,Wisler et al., 2007)
FSH	FSHR	Impaired desensitization and internalization (N431I) and β-arrestin bias (A189V) associated with mutations at the FSHR in patients with fertility disorders	(Casas-Gonzalez et al., 2012,Tranchant et al., 2011)
Angiotensin	AT_1R	Selectively engaging β-arr reduces blood pressure and increases cardiac performance; β-arr-biased agonism induced by mechanical stress	(Felker et al., 2015,Monasky et al., 2013,Rakesh et al., 2010,Violin et al., 2010)
Kisspeptin	GPR54	β-arr2 signalling promotes invasiveness through invadopodia formation in breast cancer cells; β-arr-dependent and Gq-independent signalling in GPR54 mutations associated with hypogonadotropic hypogonadism	(Goertzen et al., 2016,Szereszewski et al., 2010,Zajac et al., 2011)
Prokineticin	PKR2	Various missense mutations found in PKR2 gene in patients with Kallmann syndrome lead to G protein or β-arr bias	(Sbai et al., 2014)
Endothelin	ET_AR	Epithelian ovarian cancer: β-arr-dependent activation of oncogenic factor NFκB	(Maguire et al., 2012)
PTH	PTH_1R	β-arr pathway stimulates trabecular bone growth without inducing bone resorption	(Gesty-Palmer et al., 2006,Gesty-Palmer et al., 2009)
GLP1	GLP_1R	Role of β-arr1 in insulin secretion and in β cell proliferation; G protein-biased agonist P5 has potent antidiabetic effects	(Quoyer et al., 2010,Ravier et al., 2014,Sonoda et al., 2008,Talbot et al., 2012,Zhang et al., 2015)

Table 2: demonstrated implications of β-arrestin-dependent signalling in pathophysiological situations

Abbreviation list

α1AR, α2AR : Adrenoreceptors α1 and α2
AC2 : Adenylyl cyclase 2
AKT : Protein kinase B
AMY1R, AMY2R, AMY3R, CGRPR, AM1R, AM2R, CTR, CALRLR : Calcitonin, amylin, calcitonin gene-related peptide and adrenomedullin receptors
AP2 : Adaptator protein 2
ApelinR : Apelin receptor
ARF6 : ADP-ribosylation factor 6
ARNO : ARF guanine nucleotide exchange factor
ASK1 : Apoptosis signal-regulating kinase 1
AT1R : Angiotensin receptor type 1
β1AR, β2AR, β3AR : Adrenoreceptors β1, β2 and β3
BLT1R, BLT2R, CysLT1R, CysLT2R, OXER, FPR2/ALXR : Leukotriene receptors
BRET : Bioluminescence resonance energy transfert
cAMP : cyclic adenosine monophosphate
CCKAR, CCK1R, CCKBR, CCK2R: Cholecystokinin receptors
CRF1R, CRF2R: Corticotropin-releasing factor receptors
DP1R, DP2R, EP1R, EP2R, EP3R, EP4R, FPR, IPR, TPR : Prostanoid receptors
EC_{50} : Half maximal effective concentration
EGF : Epidermal growth factor
ERK : Extracellular signal-regulated kinase
ETAR, ETBR : Endothelin receptors
FRET : Fluorescence resonance energy transfer
FSHR : Follicle stimulating hormone receptor
Gαs : Alpha subunit of heterotrimeric G protein
Gβγ : Beta and gamma subunits of heterotrimeric G protein
GhrelinR (GHSR1a) : Ghrelin receptor
GHRHR, GIPR, GLP1R, GLP2R, SCTR : Glucagon family of receptors
GPCR : G protein-coupled receptor
GPR54 : Kisspeptin receptor
GRK : G protein-coupled receptor kinase
IκBα : nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
JNK : c-Jun N-terminal kinase
LHR : Luteinizing hormone receptor
MAPK : Mitogen-activated protein kinase
MC1R, MC2R, MC3R, MC4R, MC5R : Melanocortin receptors
MDM2 : Mouse double minute 2 homolog
MEF : Mouse embyonic fibroblast cells
MEK1 : Mitogen-activated protein kinase kinase 1
MKK : Mitogen-activated protein kinase kinase
MNK : MAP kinase-interacting kinases
MotilinR : Motilin receptor
MT1R, MT2R : Melatonin receptors
NK1R, NK2R, NK3R : Tachykinin receptors

NSF : N-ethylmelaimide sensitive fusion protein
OX1R, OX2R : Orexin receptors
OXTR : Oxytocin receptor
P38 : P38 mitogen-activated protein kinase
P90RSK : MAPK-activated protein kinase-1
PDE4D3 : cAMP-specific phosphodiesterase PDE4D3
PI3K : Phosphatidylinositide 3-kinases
PKA : Protein kinase A
PKR1, PKR2 : Prokineticin receptors
PLA2 : Phospholipase A2
PP2A : Protein phosphatase 2A
PPYR1, NPY1R, NPY2R, NPY4R, NPY5R : Neuropeptide Y receptors
PTEN : Phosphatase and TENsin homolog
PTH1R, PTH2R : Parathyroid hormone receptors
RhoA : Ras homolog gene family, member A
RNA : Ribonucleic acid
ROCK : Rho-associated protein kinase
RXFP1R, RXFP2R, RXFP3R : Relaxin family peptide receptors
SST2R, SST3R, SST5R : Somatostatin receptors
TRHR : Thyrotropin-releasing hormone receptors
TSHR : Thyrotropin receptor
V1AR, V1BR, V2R : Vasopressin receptors
VPAC1R, VPAC2R, PAC1R : Vasoactive intestinal peptide and pituitary adenylate cyclase-activating peptide receptors

Figure legend

Figure 1: Schematic representation of a G_s-coupled GPCR activation/deactivation dynamics. β-arrestins are centrally involved in all key steps.

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Highlights

- β-arrestins affect all the facets of GPCRs signalling, not just desensitization
- β-arrestins are recruited to most hormone-responsive GPCR classes
- β-arrestins control GPCR-mediated signals in intensity, time and space
- There is a close connection between β-arrestin signalling and biased pharmacology
- The understanding of β-arrestin-dependent mechanisms is rapidly evolving

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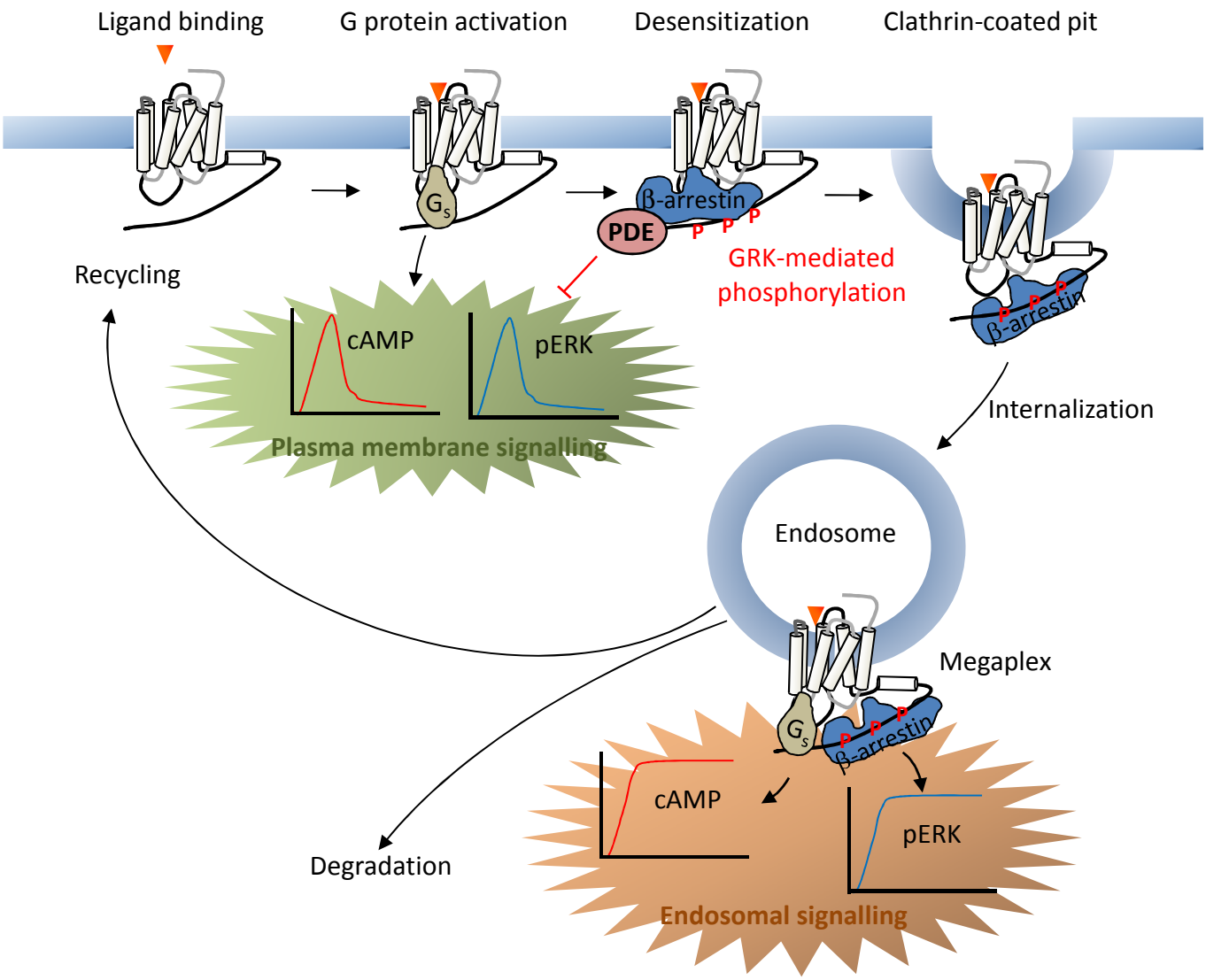

Figure 1

Reiter, E., Ayoub, M. A., Pellissier, L., Landomiel, F., Musnier, A., Trefier, A., Gandia, J., De Pascali, F., Tahir, S., Yvinec, R., Bruneau, G., Poupon, A., Crépieux, P. (2017). -arrestin signalling and bias in hormone-responsive GPCRs. Molecular and Cellular Endocrinology, 449, 28-41. . DOI : 10.1016/j.mce.2017.01.052

Highlights

- β-arrestins affect all the facets of GPCRs signalling, not just desensitization
- β-arrestins are recruited to most hormone-responsive GPCR classes
- β-arrestins control GPCR-mediated signals in intensity, time and space
- There is a close connection between β-arrestin signalling and biased pharmacology
- The understanding of β-arrestin-dependent mechanisms is rapidly evolving