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# β-arrestin signalling and bias in hormone-responsive GPCRs

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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.



## 1. 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

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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.

## 2. 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 (Fig. 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 evidence (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, 2001).

Beyond their roles in the control of desensitization and

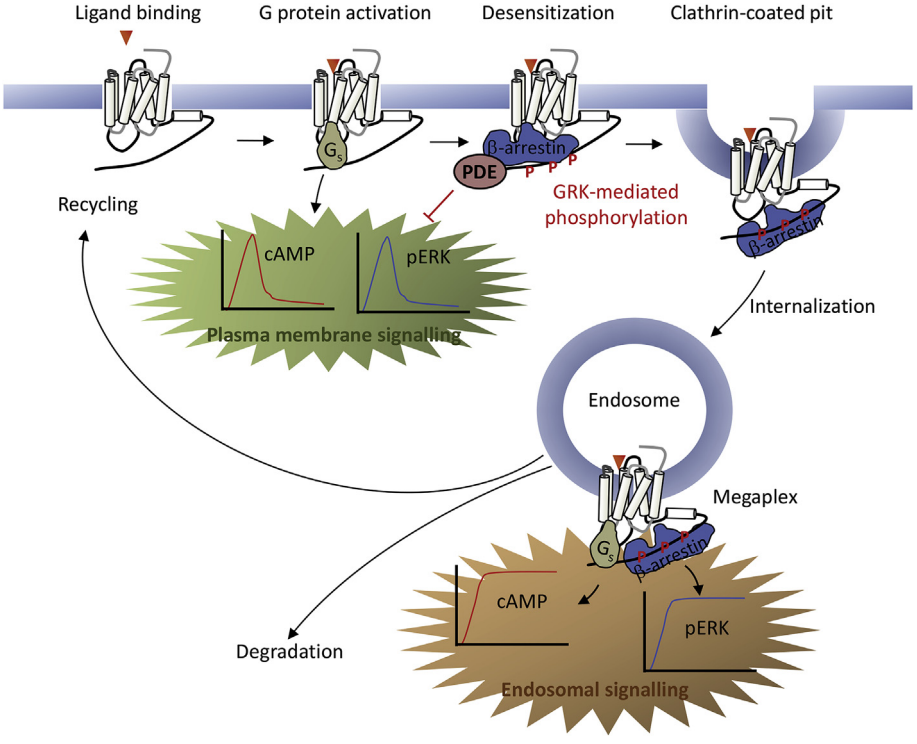


**Fig. 1.** Schematic representation of a $G_s$-coupled GPCR activation/deactivation dynamics. β-arrestins are centrally involved in all key steps.