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A Brief History of the β -Arrestins

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Abstract

Arrestins have now been implicated in the actions of virtually every G protein-coupled receptor (GPCR) for which they have been examined. Originally discovered for their role in the turnoff of visual perception, their newly discovered pleiotropic functions in the cellular and physiological actions of GPCRs not only illuminate new mechanisms of signal transduction but also offer new avenues for therapeutic utility. Below, in this introductory chapter, we provide a short historical description and synopsis of how arrestins conceptually became associated with the function of GPCRs.

Keywords

β -Arrestins; GPCR; GPCR kinases; Desensitization; Endocytosis; Signaling; selectivity/bias; Therapeutics

1. Historical Perspective of β -Arrestin Biology

Arrestins were first discovered as a major protein component of the retinal photoreceptor region and originally called the “retinal S antigen” for their involvement in uveitis [1]. Subsequent work in the visual system in the early 1980s led to the idea that the protein was involved in the turnoff of light-activated rhodopsin [2]. At that time, the relationship between the visual system machinery and receptors for hormones and neurotransmitters was not yet fully appreciated. This interesting relationship became more obvious with the cloning of the β 2-adrenergic receptor (β 2AR) in 1986, which revealed that the putative membrane topology of the β 2AR was similar to that of rhodopsin [3]. Early biochemical work with photoaffinity labeled and/or purified β 2AR had demonstrated that phosphorylation of the β 2AR by a kinase distinct from protein kinase A (PKA) might be involved in its desensitization process [4–6]. Subsequently, a purified candidate protein kinase—originally called β 2- adrenergic receptor kinase or β ARK1, and later renamed G protein-coupled receptor kinase 2 (GRK2)—was isolated from lymphoma cells lacking protein kinase A and shown to inhibit bovine brain capable of inhibiting the β 2AR activation of G protein [7]. However, as the purity of this kinase preparation advanced, its β 2AR/G

protein uncoupling activity was lost until the reconstituted mix was supplemented with purified retinal S antigen/visual arrestin [7, 8], suggesting a role for an arrestin-like protein in the regulation of non-visual GPCRs. Subsequent work in the field led to the eventual purification and/or cloning of two visual GPCR kinases (GRKs) [9,10] and five non-visual GRKs [11–15], as well as the genes for two distinct visual arrestins (arrestin 1 and 4) [16, 17] and two non-visual arrestins alternatively referred to as β -arrestin 1 or arrestin 2 and β -arrestin 2 or arrestin 3 [18, 19]. Further investigations established that GRKs and arrestins together were necessary not only to fully modulate the signaling function or “desensitization” of the β 2AR but also the signaling function of other GPCRs [20, 22]. Moreover, it was established that while these two classes of visual and non-visual accessory proteins display similar functions, specificity of action as well as tissue specificity could be demonstrated [22].

Cellular work in the early 1990s began to investigate other possible roles for the GRK/arrestin modulation of GPCRs. Following on the earlier observations that GPCRs became “desensitized” and internalized following prolonged agonist activation [23, 24], it was demonstrated that desensitized β 2AR could co-localize within the same endocytic compartment as the transferrin receptor, suggesting that GPCRs internalization might use the same mediated endocytic machinery [25]. This observation was further corroborated when it was revealed that β -arrestin 2 played an essential role in the internalization of the desensitized β 2AR, functioning as an adaptor to the endocytic machinery [26, 27]. Interestingly, tagging β -arrestins with GFP provided not only a way to assess GPCR/ β -arrestin interactions and trafficking in real time but also a foundation for the development of various cellular reporters widely used today for GPCR ligand screening [28]. Subsequent observations with different GPCRs led to the rather unexpected idea at the time that GPCR/arrestin interaction could initiate intracellular signaling cascades, distinct from the canonical G protein-mediated signals [29, 30]. Eventually, this provocative idea was further supported by the demonstration that a given ligand could bind to a given receptor and act as an agonist at G protein signaling but an antagonist for β -arrestin interactions or vice versa [31, 32].

Finally, the relevance of the visual arrestin/ β -arrestin concept was further established by demonstrating an in vivo physiological relevance for GPCR/ β -arrestin interactions. Indeed, the absence of β -arrestin 2 in mice markedly enhanced the analgesic effects of the opiate agonist morphine while concomitantly eliminating the development of morphine induced tolerance as well as the life-threatening side effects of decreased respiration and gastrointestinal function [33–35].

To use a colloquial expression, “the rest is history.” As is elegantly outlined in this collection of methodological essays, the breadth of techniques presented in this compendium speaks not only to multitude of ways in which GPCR/ β -arrestins can be studied in the context of protein/protein interactions but also in the potential functions these interactions can play in the normal and dysfunctional physiological contexts.

2. Implications of β -Arrestin for Improved Therapeutics

Since the early 2000s, the breakthrough resolution of the crystal structure of the prototypical GPCRs like rhodopsin and β 2AR [36, 37] as well as complexes of GPCRs with their G protein or β -arrestin signaling partners [38–41] has added an unprecedented level of sophistication in approaches to elucidate GPCR signaling mechanisms and developing new therapies. As case in point, the advent of molecular modeling and docking of millions of chemical structures onto the structure of GPCRs [42] combined with conventional cellular screening platforms has provided exciting new ways to develop novel receptor probes with exquisitely high affinity and specificity [43, 44]. The methodologies described in this collection of papers/essays become crucial for relating the molecular determinants underlying GPCR/ β -arrestin interactions to the experimental parameters that define a receptor's signal transduction network. Indeed, one of the most interesting and potentially significant aspects of the GPCR/ β -arrestin paradigm is the possibility to selectively target that interaction for therapeutic gain. GPCRs represent a large portion of the therapeutic landscape, but most drugs invariably have untoward side effects. While these unwanted effects have been commonly attributed to the promiscuous interaction of drugs with other GPCRs, a lack of selectivity of these agents for the distinct signaling modes of targeted receptors may significantly contribute to an unnecessary reduction in their therapeutic specificity. Our ability to now develop therapeutic agents that have improved selectivity or bias for either the G protein or β -arrestin signaling pathways is bound to produce better therapies.

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