Seven-transmembrane receptors (7TMRs), also known as G-protein-coupled receptors (GPCRs), are the single largest class of drug target; they account for up to 50% of currently marketed drugs [1]. Because they are a family of cell-surface proteins capable of binding a wide diversity of molecules that regulate nearly every physiological process, 7TMRs continue to be targets of significant therapeutic research and development. However, the conceptual framework that underlies the well-established pharmacology of 7TMRs is evolving, and questions are being raised on how recent work suggests that receptor pharmacology is much more complex and subtle than previously understood. This recent described concept of ‘ligand bias’, the ability of ligands to selectively stabilize receptor conformations that stimulate or inhibit subsets of receptor activities, has led to the understanding that receptor pharmacology is much more complex and subtle than previously understood. This review will discuss ligand bias for β-arrestin functions and how recent work suggests that β-arrestin-biased ligands might provide opportunities for the development of novel therapeutics.

Introduction

Seven-transmembrane receptors (7TMRs), also known as G-protein-coupled receptors (GPCRs), are the single largest class of drug target; they account for up to 50% of currently marketed drugs [1]. Because they are a family of cell-surface proteins capable of binding a wide diversity of molecules that regulate nearly every physiological process, 7TMRs continue to be targets of significant therapeutic research and development. However, the conceptual framework that underlies the well-established pharmacology of 7TMRs is evolving, and questions are being raised on how we can exploit 7TMR biology for the development of new therapeutics.

7TMR function is mediated and modulated through two ubiquitous and generic mechanisms: G-protein activity and β-arrestin function (Figure 1). Classic agonists (see Glossary) bind the receptor and stabilize conformations that couple to and activate heterotrimeric G proteins; this activation leads to canonical second-messenger signaling. These activated receptors also stimulate and are substrates for G-protein-coupled receptor kinases (GRKs). After phosphorylation by GRKs, receptors bind β-arrestins, which sterically interdict further G-protein signaling. This limits the G-protein signal duration, resulting in receptor desensitization. β-arrestins also scaffold receptors to membrane-trafficking machinery, and thus cause receptor internalization from the cell surface and sequestration from G proteins. Furthermore, β-arrestins scaffold numerous signaling molecules that are stimulated by receptor agonism. Thus, as β-arrestins turn off G-protein signals, they can simultaneously initiate a second, parallel set of signals [2–4].

Classically, it was thought that all 7TMR activities correlated; that is, ligand binding stimulated or inhibited all receptor functions to an equal extent [5]. Under this paradigm of ‘correlated efficacies’, any assay of 7TMR function could fully characterize all ligands of a given 7TMR as full agonists, partial agonists, inverse agonists or neutral antagonists. However, evidence accumulated over the last decade contradicts this view. The more recently described concept of ‘ligand bias’, the ability of ligands to selectively stabilize receptor conformations that stimulate or inhibit subsets of receptor activities, has led to the understanding that receptor pharmacology is much more complex and subtle than previously understood. This review will discuss ligand bias for β-arrestin functions and how recent work suggests that β-arrestin-biased ligands might provide opportunities for the development of novel therapeutics.

Glossary

Agonist: a ligand that, by binding a receptor, increases that receptor’s activity.
Antagonist: a ligand that binds a receptor without stimulating any activity. Also known as a ‘blocker’ because of its ability to prevent binding of other ligands and, therefore, block agonist-induced activity.
Correlated efficacies: when ligand binding stimulates or inhibits all receptor functions to an equal extent; thus, the relative efficacy of a ligand for any signal is identical to the relative efficacy of that ligand for any other signal.
Imperfect bias: ligand stimulation of multiple receptor activities with different relative efficacies for different signals; thus, the selectivity of the ligand is not absolute.
Inverse agonist: an antagonist that, in addition to blocking agonist effects, reduces receptors’ basal, constitutive activity.
Ligand bias: the ability of a ligand to selectively stimulate a subset of a receptor’s activities. Such ligands are known as ‘biased ligands’, ‘biased agonists’ or ‘functionally selective agonists’.
Neutral antagonist: a special case of an antagonist that neither stimulates any signals nor inhibits intrinsic receptor activity.
Partial agonist: an agonist that results in a sub-maximal response, even when receptors are fully occupied. Partial agonists can also function as ‘blockers’ by preventing the binding of more-robust agonists.
Perfect bias: ligand stimulation of one receptor activity without any stimulation of another known receptor activity.
Discovery of β-arrestin bias

β-arrestins were first characterized as components of 7TMR-desensitization machinery for the β2-adrenoceptor; as such, they limited the amplitude and duration of Gαs-stimulated cyclic adenosine monophosphate (cAMP) signals [6]. Further work showed that the two β-arrestin isoforms, β-arrestin-1 and β-arrestin-2, are universal regulators for the entire 7TMR family [7]. In addition, β-arrestins were found to promote 7TMR internalization, which either sequesters receptors from extracellular stimuli or recycles previously desensitized receptors to the cell surface for further stimulation [8]. Most recently, β-arrestins were discovered to stimulate several G-protein-independent signals, largely in pro-survival and anti-apoptotic pathways [2–4]. Thus, β-arrestins are now known to mediate three 7TMR properties: desensitization, internalization and signaling. Until recently, ligand efficacy for each of these functions was thought to be directly proportional to efficacy for G-protein activity. This was based on the earlier finding that a ligand’s relative efficacy was the same for different signals [5]. However, in light of our new understanding of signal-transduction pathways and after careful evaluation of many more ligands and receptors, it is now clear that this is not always the case; G-protein and β-arrestin efficacies can differ and can be specifically modulated under the evolving paradigm of ligand bias.

The first appreciation of 7TMR ligand bias arose from studies that demonstrated uncorrelated efficacies for different G-protein-stimulated signals in a set of muscarinic acetylcholine receptor agonists [9,10]. Although acetylcholine activates both Gαs-stimulated cAMP and Gαq-stimulated phospholipase C (PLC) responses at this receptor, these studies found several ligands that block cAMP responses but activate PLC responses. These findings challenged traditional models of receptor pharmacology [11] by suggesting that 7TMRs could adopt multiple active states. This notion was extended to β-arrestin function through the discovery of non-desensitizing agonists; compounds that induce G-protein signaling but fail to stimulate 7TMR phosphorylation, β-arrestin recruitment and receptor internalization [12–14]. These findings demonstrated that G-protein activation is not always sufficient to stimulate receptor phosphorylation and β-arrestin recruitment and contradicted the prevailing belief in correlated efficacies for G-protein stimulation and phosphorylation by GRKs. Indeed, it was soon discovered that G-protein activation is not only insufficient for β-arrestin function but can also be unnecessary; several ligands that recruit β-arrestin and/or induce receptor internalization without stimulating any detectable G-protein signaling have been identified [15–17]. Thus, for at least some receptors, β-arrestin functions, such as internalization and signaling, can be completely independent of G-protein signaling. This represents the extreme case of ligand bias, or ‘perfect bias’: ligand stimulation of one receptor activity without any stimulation of another known receptor activity. However, many biased ligands exhibit ‘imperfect bias’, where selectivity for different signaling pathways is a matter of degree (e.g. full agonism for one signal and partial agonism for a second signal [13,18]). Such ligands are more difficult to characterize but might be of considerable interest in physiological settings where subtle bias might be most beneficial. Thus, although examples of perfect bias are the most thoroughly studied, the potential utility of imperfectly biased ligands should not be ignored.

The conceptual challenge of β-arrestin ligand bias

As examples of β-arrestin ligand bias proliferate, it has become more important to understand how β-arrestin functions contribute to the full characterization of novel ligands. Mechanistically, the existence of β-arrestin bias supports a ‘conformational ensemble’ model of receptor function [19]; this model describes each receptor function as a consequence of a ligand-bound receptor’s favoring a subset of all possible receptor conformations. For unbiased ligands the subset of conformations for G-protein activation and β-arrestin coupling are identical, whereas for biased ligands these subsets differ (Figure 2). The nature of these receptor conformations is still incompletely understood. However, researchers have recently made significant progress, including the direct measurement of several examples of 7TMR conformational changes [20,21]. Importantly, these studies demonstrated distinct conformational changes for different ligands consistent with ligand bias in the context of conformational ensemble models. In addition, studies of rhodopsin structure and conformational changes have been of great utility in modeling other GPCR conformations [22]. Nonetheless, in practice we are largely limited to describing receptor conformations indirectly in terms of ligand efficacies, that is, the biological consequences of a ligand-occupied receptor. In this context, bias occurs when a ligand exhibits different efficacies, relative to a reference ligand, for two different receptor functions.

As described above, the extent of ligand bias exhibited by different receptors is likely to vary among the 7TMR
family. No apparent pattern in receptor features suggests which molecular events are required for stimulating β-arrestin function without stimulating G-protein activity. Most 7TMR efficacies are determined by the interactions of effectors, such as G proteins, GRKs and β-arrestins, with receptor intracellular loops and tails. These regions are poorly conserved across the 7TMR family and sequences conferring GRK activity or β-arrestin recruitment are incompletely defined. Thus, it is not yet possible to predict which receptors are capable of biased signaling; instead, the discovery of further examples of biased ligands might rely on the methodical evaluation of large numbers of 7TMR ligands. In time, we might even discover that all 7TMRs are capable of β-arrestin-biased signaling.

A further complication of translating the concept of β-arrestin bias into novel drug candidates is the complexity of 7TMR signaling networks. Because β-arrestins both suppress G-protein signals and mediate β-arrestin signaling, it is difficult to predict how the biological effects of biased ligands might differ from those of unbiased ligands. For example, β-arrestin knockout or siRNA silencing both prolong G-protein signaling and abrogate β-arrestin signaling [23]. This necessitates carefully designed experiments for distinguishing the biological effects of specific signaling mechanisms that could be selectively stimulated by biased ligands. Another approach is the generation of mutant receptors that do not stimulate G proteins but that retain the ability to recruit β-arrestin and stimulate β-arrestin-mediated signaling and receptor internalization. Such receptor mutants are intrinsically biased, yielding only β-arrestin functions even in response to traditional full agonists [15,24,25]. Both β-arrestin ablation and receptor mutants have been used for elucidating β-arrestin signaling but such experiments imperfectly mimic true biased ligands. In general, assessment of biased ligands as therapeutic leads might first require the discovery of candidate-biased ligands for testing in physiological systems. Data from experiments in more physiological systems have begun to emerge [26], but it is clear that extensive work remains to be done in defining how β-arrestin bias can aid drug-development efforts.

Examples of β-arrestin-biased ligands

The number of ligands shown to exhibit β-arrestin bias has increased in recent years. The most startling of these discoveries have been examples of perfect bias; that is, ligands that stimulate β-arrestin functions but that completely fail to induce G-protein signaling, or vice versa. These examples have grown to comprise a diverse list of receptors and ligands, including the angiotensin II type 1 (AT1) receptor [15], β2-adrenoreceptor [21], CCR7 [14] and CXCR4 [27] chemokine receptors, μ-opioid receptor [12] and type 1 parathyroid hormone (PTH1) receptor [17,28]. We will review several of the most extensively studied receptors that exhibit β-arrestin ligand bias in hopes of highlighting the potential for ligand-bias studies to foster novel 7TMR drug development.

μ-Opioid receptor

The first receptor shown to exhibit β-arrestin-biased ligand binding was the μ-opioid receptor, which is the target for both endogenous enkephalin peptides and opiate drugs such as morphine. Early studies demonstrated G-protein agonism and receptor internalization for enkephalins and the opiate etorphine but found a striking lack of receptor internalization for the opiate agonist morphine [29]. This was explained by morphine’s very weak ability to stimulate μ-opioid receptor phosphorylation and to recruit β-arrestin [30]. This finding established β-arrestin function as an efficacy distinct from G-protein activation and is an example of
negative β-arrestin bias; in comparison to other agonists, such as enkephalins, morphine stimulates β-arrestin function disproportionately weakly compared to its stimulation of G proteins. However, in mice that lack β-arrestin-2, morphine-induced analgesia is amplified and prolonged, indicating that, despite its bias, morphine stimulates β-arrestin-mediated desensitization [31]. This suggests that even more strongly biased ligands that completely circumvent β-arrestin-mediated desensitization might offer enhanced analgesia.

Interest has grown in taking advantage of ligand bias at the µ-opioid receptor for drug-development purposes in hopes of separating the therapeutic efficacy and side effects of opiate drugs [32]. Recently, a novel µ-opioid receptor ligand that is more negatively β-arrestin biased than morphine was discovered [33]. This compound, named herkinorin, might provide a lead toward developing biased-ligand drugs that increase opiates' analgesic effects. Furthermore, such biased ligands might avoid common opiate side effects, such as tolerance, respiratory suppression and constipation, which have been shown to be mediated by β-arrestin-2 [34,35].

**Angiotensin II type 1 receptor**

The AT1 receptor regulates blood pressure and electrolyte homeostasis and is the target of angiotensin-receptor blockers (ARB's, such as valsartan and losartan) for the treatment of hypertension. The AT1 receptor has also been a major focus for the investigation of β-arrestin bias. Angiotensin II (AngII) canonically signals through Gq-mediated activation of PLC and robustly induces receptor phosphorylation by GRKs and recruitment of β-arrestin. β-arrestin recruitment to the AT1 receptor desensitizes Gq signaling, internalizes the receptor and induces β-arrestin signaling independently of G proteins [23,36,37]. The distinct nature of β-arrestin signaling is clearly demonstrated by the discovery of a perfectly biased ligand, Sar1, Ile4, Ile8-AngII (SII) [18], that stimulates β-arrestin signals, such as ERK1/2 activation, in the absence of detectable G-protein agonism [15,38]. This SII-stimulated signaling confirms that β-arrestin-coupling and G-protein-activating receptor conformations are distinct (Figure 2a). Such G-protein-independent β-arrestin signaling has also been shown with mutant receptors that do not couple to G proteins and with siRNA silencing of β-arrestin2 [15,38]. Furthermore, G-protein-independent effects mediated by the AT1 receptor have also been demonstrated in vivo. Transgenic overexpression of a mutant AT1 receptor that does not couple to G proteins in the mouse heart leads to cardiac hypertrophy and bradycardia [25]. Although not specifically addressed by the authors, it is possible that these effects are β-arrestin mediated. However, it is unclear what relationship these results might have to the very different situation that results when β-arrestin-biased AT1 receptor ligands, such as SII, act on endogenous receptors. Strikingly, SII has been found to induce contractility via β-arrestin signaling in isolated cardiac myocytes [26], suggesting that β-arrestin-biased ligands will have significant effects on cardiac function.

To date, several of the signaling pathways shown to be activated by SII, or by other activators of β-arrestin-mediated signaling, appear to be pro-survival, cytoprotective and/or proliferative. These include Src, ERK1/2, Akt and PI3K [2–4]. Indeed, β-arrestin signaling appears to be anti-apoptotic for a variety of receptors [39]. This has led to the speculation that SII-like compounds, which, like ARBs, are antagonists for canonical G-protein signals but are also agonists for potentially beneficial β-arrestin signals, are worthy of further investigation for drug-development programs [40] (Figure 3).

**Type 1 parathyroid hormone receptor**

The PTH1 receptor regulates serum calcium homeostasis and bone metabolism. In addition to the endogenous ligands parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP), several biased ligands have been synthesized. The first of these were PTHrP derivatives modified or truncated at the first amino acid: PTHrP(2–36) and Bpa1-PTHrP(1–36) [28]. These modified peptides preserved PTHrP's agonism for Gs-mediated...
cAMP but lost both Go- and Gq-mediated stimulation of PLC and β-arrestin recruitment and desensitization. These ligands are thus biased toward Gq-activation relative to both Go and β-arrestins. Later work discovered that a PTH derivative, described as an inverse agonist for Gq-coupled signaling (D-Trp12, Tyr34(PTH(7–34))) [41], was able to recruit β-arrestin and stimulate β-arrestin signaling in the absence of Gα- or Gq-stimulated signals [17]. Thus, there exists a range of biased ligands for the PTH1 receptor: For the known PTH1-receptor-mediated signal pathways (Gs, Gq and β-arrestins), there are ligands stimulating all three (PTH and PTHR-P), Gα only (PTHrP2–36) and Bpa-1-PTHrP(1–36)) and β-arrestin only (D-Trp12, Tyr34(PTH(7–34))) (Figure 2b).

The biologically active PTH fragment PTH(1–34) is used clinically for treating osteoporosis under the name Forteo® (teriparatide) [42]. Unlike first-line bisphosphonate, calcium and/or vitamin D therapies, which inhibit bone resorption, PTH(1–34) induces anabolic bone formation. However, it is unclear how each of the PTH1 receptor’s signaling pathways contributes to this effect or whether any of the β-arrestin-biased ligands might be superior to PTH(1–34) in terms of selective stimulation of the relevant osteogenic signals. Such a result could point the way toward developing novel PTH1-receptor-targeted therapies by identifying the relevant signaling pathways that need to be stimulated or inhibited.

Developing β-arrestin therapeutics

A critical dilemma facing our efforts to discover further examples of β-arrestin-biased ligands is how best to detect and quantify bias. In practice, ligand bias is defined operationally by the methods used to characterize receptor functions. For G-protein function there are many well-established assays with high sensitivity and specificity, and robust high-throughput systems are available for any 7TMR of interest [43]. However, there are far fewer methods for assessing β-arrestin efficacy. These include measurements of receptor phosphorylation, β-arrestin translocation to receptors and β-arrestin functions. Measures of β-arrestin functions include receptor desensitization and internalization and β-arrestin-dependent signals such as ERK1/2 activation. Receptor desensitization and internalization can be difficult to interpret because these effects can occur through both β-arrestin-dependent and β-arrestin-independent mechanisms. Similarly, ERK1/2 activation can occur through many pathways, necessitating careful controls to ensure reliable measurement of β-arrestin signals. Thus, the simplest assays of β-arrestin efficacy are measures of β-arrestin translocation to receptors. This is usually measured via fluorescently tagged β-arrestins monitored with either microscopic imaging of β-arrestin redistribution to activated receptors [44] or with fluorescence resonance energy transfer (FRET) or bioluminescence resonance energy transfer (BRET) assays that detect the interaction of β-arrestins and receptors [45,46]. Such assays offer the advantage of being intrinsically specific for β-arrestin and the 7TM of interest. However, these assays suffer from limited sensitivity. Unlike measurements of G-protein or β-arrestin signals, which are enzymatically amplified, β-arrestin recruitment assays operate stoichiometrically as a function of the proportion of receptors bound to β-arrestin. Thus, it can be very difficult to detect weak partial agonists for β-arrestin recruitment.

β-arrestin ligand bias is tested via a comparison of the relative efficacies of ligands for G-protein read-outs and β-arrestin read-outs. Any compound with significant efficacy for both assays can serve as a reference ligand; all other compounds are measured against this reference compound. Compounds that exhibit equivalent relative efficacies are unbiased; for example, a compound with 50% efficacy in both G-protein and β-arrestin assays is a traditional partial agonist. Compounds with significantly different relative efficacies are biased; for example, a compound with zero efficacy in a G-protein assay but with 100% efficacy in a β-arrestin assay is perfectly β-arrestin biased. The ratio of relative efficacies can be considered a ‘bias factor’; a single parameter for ranking putative biased ligands. Bias factor is a valid measure of ligand bias as long as both G-protein and β-arrestin assays are within a linear dynamic range. Low sensitivity or assay saturation of either assay can erroneously report bias. Nonetheless, with appropriate diligence, screening for β-arrestin-biased ligands is a very achievable goal, particularly in light of recent advances in high-content screening.

Of particular note is the fact that the myriad 7TMR ligands that have been subject to drug-development efforts have traditionally been assayed only for receptor-binding and G-protein-stimulation characteristics. There might already exist in ligand compound libraries examples of β-arrestin bias of considerable interest, unremarkable for now solely because they have not been assessed for β-arrestin functions. We expect that, as interest in β-arrestin signaling and ligand bias grows, both extant and novel ligand libraries will be tested for β-arrestin function as well as G-protein function. In all likelihood, the number of receptors known to have biased ligands will proliferate.

If we are to generate new synthetic and biological agents, the identification of and improvement upon biased ligands will require extensive efforts. Traditional 7TMR drug-lead identification and optimization efforts are already constrained by parameters for ligand affinity, G-protein efficacy, pharmacokinetics and toxicity. The addition of ligand bias as a constraining parameter will push ‘hit rates’ lower than they already are. Furthermore, because the differences between biased and unbiased receptor conformations are likely to be very subtle, the chemical differences between biased and unbiased ligands might also be quite subtle. Thus, identification and optimization of biased ligands might require increasingly diverse chemical libraries during both lead-identification and lead-optimization efforts. Recent advances in increasing chemical diversity will be important for overcoming these challenges [47], as will the rapidly advancing field of molecular modeling [48].

The possible clinical utility of β-arrestin-biased ligands rests on the potential for β-arrestin function as a therapeutic target. Early studies suggest that β-arrestin signaling is a valuable target for some receptors, such as the AT1 receptor [26]. β-arrestin-biased ligands, such as SII (described above), might function as ‘super-ARBs’ that decrease blood pressure by blocking G-protein signals while stimulating potentially beneficial β-arrestin signals.
Similarly, one can envision ’super β-blockers’ that block β-adrenoceptor G-protein signals while stimulating β-arrestin signals. Conversely, negatively β-arrestin-biased ligands such as herkinorin for the μ-opioid receptor might be useful as ‘super-agonists’ that hyper-stimulate G-protein pathways by circumventing β-arrestin-mediated desensitization. These compounds should also exhibit qualitatively distinct physiological responses because they will not activate β-arrestin signaling pathways.

Validating these pharmacological behaviors for drug development will probably depend on the tools described above: β-arrestin-knockout mice, mutant receptors that do not simulate G-protein signals and siRNA-mediated β-arrestin silencing. Interrogating clinically interesting 7TMRs with these techniques will clarify the benefits and drawbacks of targeting selective activation of G-protein or β-arrestin function with biased ligands. Given the diversity of 7TMR function, it is probable that β-arrestin-biased ligands will offer significant clinical advantages for several target receptors. The identification of these receptors and the validation of β-arrestin signaling as a therapeutic target promises to be an exciting field of research. Indeed, β-arrestin-biased ligands might offer significant, untapped advantages for drug-development programs willing to pursue them.

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