EDITORIAL

Brave New World? Arrestin Pathway Bias in Drug Design

Bradley T. Andresen[1,2,3,*] and Louis M. Luttrell[4,5]

[1]Department of Internal Medicine, Division of Endocrinology, University of Missouri; [2]Department of Medical Pharmacology and Physiology, University of Missouri; [3]Harry S Truman Veterans Affairs Medical Center; and [4]Department of Medicine and Biochemistry & Molecular Biology, Medical University of South Carolina; [5]Ralph H. Johnson Veterans Affairs Medical Center

The phenomenon of G protein-coupled receptor (GPCR) ligand 'bias', the ability of an agonist to activate (or inhibit) only a part of its receptor's downstream signals, has been recognized for over 15 years [1]. 'Bias', or functional selectivity, can take many forms; from 'reversal of potency', where two ligands activate different signaling pathways with opposite potency, to outright 'reversal of efficacy' where a ligand that antagonizes one pathway activates another. Examples of functional selectivity extend across the full spectrum of GPCR signaling. Most of the initial work in the area focused on the ability of certain drugs to bias receptor coupling to different heterotrimeric G protein pools, e.g. favoring cAMP production or phosphatidylinositol hydrolysis, e.g. *see* [2]. This early work established two key points in GPCR pharmacology; that GPCRs are capable of assuming multiple 'active' states, and that chemically distinct ligands can activate receptors in qualitatively different ways. More recent work has explored biased ligands that dissociate the two major consequences of GPCR activation; heterotrimeric G protein activation and arrestin-mediated desensitization. With the recognition that arrestin binding not only uncouples the receptor and G protein, but also initiates signaling from receptor-arrestin 'signalsomes' [3], this work has come to define a new type of bias; ligands that select between two major, and mutually exclusive, GPCR signaling states. Both G protein pathway-selective, i.e. non-desensitizing, and arrestin pathway-selective, i.e. G protein-independent, biased agonists have now been described for a number of GPCRs. Such biased agonism is an emerging concept in drug design, and carries with it both the potential for new, more efficacious drugs, and the risk that incomplete characterization of drug efficacy may lead to unintended side effects.

The collection of articles that follow are intended to provide a brief introduction to biased agonism and to illustrate some of the current and potential roles that arrestin pathway-selective biased agonists may play in medicine. Besides providing a detailed topic review, each paper highlights a different facet of biased signaling. The first paper by B. T. Andresen introduces the concept of biased agonism and defines some of the newer terms finding their way into the pharmaceutical lexicon. In telling the story of carvedilol (Coreg®), a β-adrenergic receptor blocker with proven survival benefit in congestive heart failure that was subsequently shown to possess arrestin pathway-selective agonism [4,5], Dr. Andresen makes the point that biased ligands have actually been in the clinic for a long time. We just did not recognize it. Traditional high throughput methods that rely on single functional readouts to categorize ligand efficacy are not designed to capture ligand bias, yet bias may be more the norm than the exception in GPCR pharmacology. Whether carvedilol, which has proven safe and effective over decades of use, owes some of its some of its clinical efficacy to arrestin pathway activation is unknown, but it certainly raises the question of whether future β blockers should be designed to incorporate, or avoid, activation of arrestin signaling.

The article by D. A. Zidar discussing natural biased agonism of chemokine receptors [6,7] makes the somewhat humbling point that the phenomenon of biased agonism is not merely a product of synthetic pharmacology. It turns out that Nature has been exploiting ligand bias to control leukocyte trafficking and immune responsiveness far longer than pharmaceutical scientists have been working to discover clinically useful biased drugs. This has obvious implications for chemokine signaling where there are overlapping affinities and more than twice the number of endogenous chemokines than chemokine receptors. Does this simply reflect a need for redundancy in a critical physiological system, or is ligand bias a common solution to the need for fine regulation in complex signaling systems? How many other endogenous substances are biased agonists, and how might pharmaceuticals capitalize on the fact that biological systems may already be poised to respond selectively?

D. G. Tilley raises other important points. The angiotensin AT_1 receptor is the most intensively studied GPCR with respect to arrestin-dependent signaling, and recent unbiased phospho-proteomic surveys of the response to [Sar^1-Ile^4-Ile^8]-Ang II, an arrestin pathway-selective AT_1 receptor agonist [8,9], have revealed startling complexity, to the point that the G protein-independent signaling network may ultimately prove to be as extensive as that regulated by classical G protein signaling. Dr. Tilley discusses biased AT_1 receptor agonism in the cardiovascular system and evidence that arrestin pathway-selectivity may be advantageous in the treatment of cardiac disease. He also discusses a surprising 'off-target' effect of the peroxisome proliferator-activated receptor gamma agonist, troglitazone, an oral hypoglycemic thiazolidinedione that was removed from the market over 10 years ago, that turns out to be an arrestin-selective AT_1 receptor biased agonist [10]. Ligand bias is not only commonplace in natural and synthetic pharmacology; it also turns up in the most unexpected places!

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Finally, B. N. Bohinc and D. Gesty-Palmer discuss biased agonism of the type 1 parathyroid hormone (PTH) receptor, and how G protein-dependent and arrestin-dependent signaling pathways contribute to the regulation of bone turnover. They describe recent work using an arrestin pathway-selective PTH_1 receptor agonist that appears to dissociate the ordinarily coupled effects of PTH on bone-forming osteoblasts and bone-resorbing osteoclasts in a manner that allows for selective acceleration of bone formation [11]. Results like these offer early proof of principal that biased agonists can be used to obtain physiological responses *in vivo* that cannot be achieved using conventional agonist or antagonist ligands.

As the new decade begins, we seem poised on the brink of a brave new world of GPCR targeted pharmaceuticals that will exploit the natural phenomenon of ligand bias to tailor drug efficacy in a manner that enhances therapeutically beneficial signals while blocking deleterious ones [12]. And the future may be nearer than we think. Biased agonism is attracting attention throughout the pharmaceutical industry, and arrestin pathway-selective compounds are beginning to enter clinical trials, with a biased AT_1 receptor agonist being studied in acute heart failure and a bradykinin receptor biased agonist under development for small cell lung cancer. Meanwhile ever more sophisticated screening approaches designed specifically to identify biased agonists are coming on-line. Consequently, there is a high probability that by the time the decade is out, biased drugs will be finding their way into the clinic, this time not by accident, but by design.

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Bradley T. Andresen
(Guest Editor)
Harry S Truman VAMC, University of Missouri
Department of Internal Medicine
Division of Endocrinology
Department of Medical Pharmacology &
Physiology, Harry S Truman VAMC
Research, 800 Hospital Dr. Columbia
MO 65201
Columbia
Tel: 573-814-6000 x53726
Fax: 573-814-6551
E-mail: andresenb@missouri.edu