Chapter 2
Functional Selectivity: Theoretical Considerations and Future Directions

Terry Kenakin

Abstract The selective activation of receptors by some agonists to emphasize some but not all aspects of the receptor signaling capability was proposed on theoretical grounds in 1995 because of data showing reversal of relative orders of potency for different stimulus pathways linked to a single receptor. These data precluded the notion that all agonists produce a single receptor active state. Since that time, a number of different lines of evidence indicate that ligands can bias receptor toward different pathways in cells. Conformational selection within the ensemble of conformation receptors formed during normal function theoretically is capable of producing functional selectivity; this chapter discusses the thermodynamic nature of this effect. Finally, although functional selectivity is a well-documented pharmacological phenomenon duplicated in many laboratories, it is still unclear whether it can be harnessed to produce therapeutically unique effect; it is hoped that studies in translational medicine with functionally selective ligands will furnish the link to therapy.

Keywords Receptor theory, Functional selectivity, Receptor signaling

2.1 Introduction: Linear View of Efficacy

The concept of agonist efficacy was required when it was observed that agonist occupancy curves and functional response curves did not coincide with respect to location along the concentration axis (functional curves are shifted to the left of occupancy curves). To accommodate this, it is necessary to invoke some property of the agonist operative in the production of tissue response, specifically a property of the agonist variously referred to as “intrinsic activity” (1), efficacy (2) and intrinsic efficacy (3). These were not terms rooted in physiology but rather were mathematical

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terms inserted to make experimental results coincide with theory. A more physiological approach yielded the standard that largely has replaced these early theories, namely Operational Theory where efficacy and tissue sensitivity is quantified by a term $\tau$ \(^{(4)}\). Although the settings for these efficacies have changed over the years, the basic assumption driving all of them has not, namely that efficacy stems from a single activated receptor state. This assumption has furnished the basis for receptor and drug classification such as agonist potency ratios. The necessity for invoking functional selectivity as described in this volume stems from violations of these predictions of classical receptor theory.

When considering equiactive concentrations of agonist under null conditions, it is assumed that the ability of each agonist to produce response is subject to identical cellular constraints leaving the difference in potency to be solely due to molecular features controlling ligand affinity and efficacy. If this premise is violated, then the resulting potency ratio loses this immutable property of being dependent on chemical features of the agonists and takes on tissue-specific characteristics. This can be illustrated by analyzing potency ratios for agonists at different stages of stimulus–response coupling. Figure 2.1 shows the effects of $\beta$-adrenoceptor agonists on two cardiac functions in rat atria that are both mediated by elevation of cytosolic cyclic AMP through the same receptor activation process \(^{(5)}\). At some point in the cell, the two processes utilize the cyclic AMP to yield positive inotropy (increased strength of contraction) and the other to elicit lusitropy (increased rate of relaxation). It also is observed that the lusitropic response is more sensitive to agonist stimulation probably because of a more efficient coupling of the relaxation mechanism to elevated cyclic AMP. It can be seen in Fig. 2.1 that relative potency ratios of two $\beta$-adrenoceptor agonists, isoproterenol and pirbuterol, yield the same relative potency when each is compared within the same stimulus–response pathway. This is consistent with equal ratios of $\tau$ since this term reflects the efficacy of the agonists (a constant molecular term), the receptor density (constant for both agonists since testing is done in the same tissue), and $K_E$ (reflecting the efficiency of coupling of receptors to the response cascade, which is common for the two agonists when the same pathway is compared).

When relative potencies are compared across two different stimulus–response coupling cascades, then different $K_E$ values for the response are operative. It can be seen that when this prerequisite is violated (compare relative potency for inotropy vs. lusitropy), the potency ratio is much different and not reflective of only agonist efficacy. However, within a given pathway (inotropy or lusitropy), potency ratios agree, a finding consistent with each agonist producing a single receptor active state. In general, such potency ratios have been very consistent for receptor and agonist classification over the years, since the definition of efficacy by Stephenson \(^{(2)}\) up to approximately 10 years ago. What has changed since that time is that the number of vantage points to view receptor activation has greatly increased with improving technology. Now there are many methods available to measure agonist interaction with the receptor and the resulting change in receptor behavior beyond simple organ response (i.e., guinea pig ileal contraction as was available to Stephenson), and these increased vantage points have shown an astounding
The coupling of cardiac β-adrenoceptors to adenylate cyclase which, in turn, activates stimulus–response systems to increase cardiac inotropy and myocardial relaxation rate. The coupling is more efficient for relaxation than it is for inotropy, therefore agonists such as isoproterenol (diamonds) and pirbuterol (triangles) are more potent for lusitropy (relaxation). Within a given stimulus–response cascade, potency ratios are preserved in agreement with receptor theory predictions (tissue effects cancel). However, if this is violated and potencies are compared across stimulus–response coupling cascades the potency ratio is different.

The other important observation is the fact that various receptors have been shown to be pleiotropic with respect to the number of G-proteins with which they interact (particularly with Family B (secretin) receptors). This phenomenon allowed some of the first
early opportunities to quantitatively measure more than one consequence of receptor activation by an agonist, namely the effect on separate G-protein pathways.

2.2 Multiple G-Proteins and Functional Selectivity

Although the most simple model dictates that a receptor couples monotonically to a single signaling pathway, there is no a priori reason for this to be the case for all receptors. Moreover, the demonstration that receptors pleiotropically couple to multiple G-proteins suggests that multiple coupling with differential signaling is possible. An early formal model depicting such multi receptor coupling behavior is based on two G-proteins interacting with one receptor (6) – see linkage model schematic Fig. 2.2. Intrinsic to such models is the fact that receptor species bound to ligand and/or G-proteins are energetically different than those that are not. Therefore, given two G-proteins, G₁ and G₂, the energy required to form the two ternary species ARG₁ and ARG₂ will fundamentally be different. This furnishes thermodynamic reasons for a given ligand to not be equally adept at producing two such ternary species. The same argument applies to different spontaneous receptor/G-protein complexes, an idea supported by the fact that receptors have different intrinsic affinities for different G-proteins biochemically. The model also fits with the notion that proteins adopt a variety of conformations in accordance to variations in thermal energy (7–12). For example, mutation data, such as that reported for the α₂-adrenoceptor, indicate that multiple receptor conformations are able to activate G-proteins, i.e., there can be multiple receptor active conformations. The model shown in Fig. 2.2 accommodates

\[
\frac{[\text{ARG}_1]}{[\text{R}_{\text{total}}]} = \frac{\alpha_L([L]/K_A)([G_1]/K_1)}{[L]/K_A ([L][1+\gamma[G_1]/K_1+\beta[G_2]/K_2]+1)}} + \frac{\alpha_R([R]/K_A)([G_1]/K_1)}{[R]/K_A ([R][1+\gamma[G_1]/K_1+\beta[G_2]/K_2]+1)}}
\]

**Fig. 2.2** Model of one receptor interacting with two G-proteins (G₁ and G₂). The affinity of the receptor differs for each G-protein (K₁ and K₂) as does that of the ligand-bound receptor (γK₁, βK₂). The receptor forms the active state of the receptor through selective affinity (α). The equation for production of one of the ternary complex species can be used to demonstrate how different agonists can traffic stimulus to different G-proteins and thus how reversals in potency ratios for agonists can occur through selective values of β and γ. This model was presented on theoretical grounds six years before the first experimental evidence to show such behavior was described in the literature (6).
this by the presence of specific parameters $\gamma$ and $\beta$, which denote the possibility of differing affinities of the ligand-bound receptor for each G-protein. Interestingly, the model also predicts that different ligands have the capability of actually reversing their relative potency for different G-proteins (6).

The link between differential G-protein coupling and receptor conformation comes from mutation study data indicating that different regions of the receptor interact with different G-proteins. Under these circumstances, it would be highly unlikely that different receptor conformations would expose different regions of the receptor protein in identical ways. The corollary to this idea then is that different receptor conformations in systems that couple to multiple G-proteins would lead to differential activation of the G-protein pathways. The only theoretical piece missing to link these ideas to ligand functional selectivity is the ability of ligands to stabilize different receptor conformations.

A model of efficacy proposed by Burgen (13), namely conformational selection, is useful in imagining the interaction of a ligand with multiple receptor conformations. Burgen’s view is that ligands stabilize various conformations by having selectively higher affinities for them (these will preferentially be stabilized). In turn, the preferential stabilization of some conformations in a system of freely interchangeable conformations necessitates that favored conformations will be formed at the expense of other conformations (Le Chatelier’s principle, ‘… If a dynamic equilibrium is disturbed by changing the conditions, the position of the equilibrium moves to counteract the change…’). Therefore, when a ligand enters a collection of conformations (to be referred to as an ensemble), it could, by selective micro-affinities, create a new preferred ensemble (Fig. 2.3). Interestingly, since

Fig. 2.3 Histograms depicting the relative abundance of receptor conformations for a receptor at rest (left panel) and in the presence of a ligand that has different affinities for the various states (right panel). In the latter case, the conformations for which the ligand has high affinity are stabilized and therefore enriched at the expense of other conformations. The composition of the new collection of conformations depends upon the molecular structure of the agonist; therefore, there is no a priori reason to suppose that the same ligand-bias will be formed by every agonist.
multiple conformations are involved, it need not be that each type of ligand would stabilize an identical ensemble of conformations. In fact, since affinity is specific to chemical structure, it might be postulated that different ligands would not form identical ensembles, i.e., that ligands would produce different bias in the receptor conformation that subsequently interacts with the cell (14).

It can be shown that a ligand with varying affinities for a range of receptor conformations necessarily will change the composition of the conformational collection through binding. Assume an ensemble of receptor conformations \( R \) (denoted as the root “inactive” state) to \( R_i \). It can be shown that the fraction of receptors not in the \( R \) state in the absence of a ligand is given by (15):

\[
\rho_{\text{nonR}} = \frac{\sum_{i=1}^{n} L_i}{1 + \sum_{i=1}^{n} L_i}
\]  

(2.1)

Where \( L_i \) to \( L_n \) are the allosteric constants for the various states (\( L_i = [R_i]/[R] \)). In the presence of a ligand \( A \) having an affinity of \( K \) for \( R \) and \( \psi_i K_i \) to \( \psi_k K_k \) for each of the other states, this expression changes to:

\[
\rho_{\text{nonR}} = \frac{\sum_{i=1}^{n} L_i + [A]/K \sum_{i=1}^{n} \psi_i L_i}{[A]/K \left(1 + \sum_{i=1}^{n} \psi_i L_i \right) + \left(1 + \sum_{i=1}^{n} L_i \right)}
\]  

(2.2)

It can be seen that (2.2) reduces to (2.1) (i.e., there will be no change in the make-up of the conformational ensemble) only if \( \psi_i \) to \( \psi_k = 1 \), i.e., only if the affinity of the ligand for every single conformation is identical. If this is not the case, then the fraction of conformations different from \( R \) in the absence and presence of a ligand will change. By definition, this means that the binding of the ligand will change the nature of the ensemble of the receptor conformations present.

Thermodynamic and theoretical predictions indicate that ligands have the ability to stabilize different receptor conformations, and that these conformations interact with multiple components in the cell membrane (16). In addition, the expectation would be that if these components interact with different regions of the receptor protein, then heterogenous interaction with differing conformations would result. This puts all of the theoretical pieces in place to describe ligand-specific functional selectivity. At this point in time, it remained for an experimental system to combine these various elements to demonstrate this effect. Early data to suggest this came from studies on the PACAP receptor, and this led to the first formal mechanistic model of ligand-specific functional selectivity (17); this model is shown in Fig. 2.4a. The model, formally identical to the one shown in Fig. 2.2, was invoked to describe a particularly striking experimental phenomenon seen in the literature with PACAP receptors, a pleiotropic receptor that activates pathways to elevate cyclic AMP and IP_3. Specifically, it was seen that two PACAP peptide fragments
**Fig. 2.4** Theoretical model of biased agonism (17) based on a one-receptor/two G-protein model. The first data to support this model were reported for PACAP receptors where reversed relative potencies of PACAP_{1-27} and PACAP_{1-38} are clearly inconsistent with a single receptor state produced by these two agonists (model from (17); data from (18)).

/PACAP_{1-27} and PACAP_{1-38}/ produced elevated cyclic AMP and IP_3 in cells but the relative potency of these two agonists for these pathways was reversed (18). Thus, the relative efficacy of PACAP_{1-27} for cyclic AMP elevation is higher than that for PACAP_{1-38} but lower for elevation of IP_3. This phenomenon is not compatible with these agonists producing a single active state of the receptor that goes on to activate these two pathways. In contrast, it suggests that PACAP_{1-27} produces an active state with higher efficacy for cyclic AMP stimulus components (relative to PACAP_{1-38}) and that PACAP_{1-38} produces an active state with higher efficacy for IP_3 stimulus components.

The model depicted in Fig. 2.4 is sufficient to describe the differential signaling properties of PACAP_{1-27} and PACAP_{1-38}, but no doubt other models are capable of doing this. The more important outcome of the analysis of the PACAP data is the demonstration of total inconsistency of such behavior with a single receptor active state model of agonist function. These data provided a serious question to the assumption that agonists form only one receptor active state to induce response but it should be noted that the conceptual thread described here is not the only one questioning the linear concept of agonist efficacy (vide infra).
This phenomenon originally was labeled as “stimulus trafficking” when first described (17) but subsequently has been referred to in the literature by a number of labels including “biased agonism,” “collateral efficacy,” “receptor-based functional selectivity,” “conformation-based functional selectivity,” and simply “functional selectivity.” In subsequent years, versions of this phenomenon, namely differential signaling by different agonists acting on the same receptor, also have been described in a variety of settings beyond multiple G-protein activation including desensitization, phosphorylation, receptor internalization, and, recently and notably in β-arrestin/receptor interactions (19–25). Also over the past decade, advances in technology have led to independent data to support the notion that different ligands stabilize different conformations of the same receptor (26–30).

2.3 Links to Established Allosteric Mechanisms

The previous discussion is concerned with ligands that bind in special ways to the receptor to produce an active effect. However, there is no mechanistic difference between this effect and long established models describing allosteric effects of molecules, i.e., standard allosteric molecules such as muscarinic modulators that bind to receptors to stabilize certain conformations that have special properties with respect to their interaction with natural ligands. The operational differences between these established mechanisms and functionally active ligands may involve the geography of binding (i.e., functional antagonists may or may not bind to the natural orthosteric endogenous agonist binding site), and the fact that the allosteric effect is expressed through an active receptor property (functional agonism) as opposed to modification of the effects of other ligands (allosteric modulation). However, the lines become blurred in these distinctions with allosteric agonists such as alcuronium where effects on endogenous agonists are mixed with a direct agonism by the allosteric ligand (31).

Functional selectivity is remarkably similar to classical allosteric modulation. Thus the binding of an allosteric modulator can impose functional selectivity on endogenous agonism through bias of the conformations possible with the binding of the endogenous agonist. For example, in systems containing CRTH2 receptors, the allosteric modulator Na-tosyltryptophan causes the natural agonist prostaglandin D2 to change from Gi and β-arrestin activation to solely Gi-activation (with no concomitant β-arrestin interaction; (32)). Similarly, the allosteric modulator AMD3100 blocks natural agonist (SDF-1α)-mediated chemotaxis via CXCR4 receptor but not the effects of peptide fragments RSVM and ASLW (33). Also, the natural agonist neurokinin A acts via NK2 receptors to activate Gs and Gq, while the allosteric modulator LP1805 changes this pattern to one of enhanced Gq activation and blockade of Gs activation (34). The key to these effects is the fact that an allosteric mechanism allows the receptor to be permissive and edit the effects of other ligands by cobinding with them. The relationship between functional agonism and classical allosteric mechanisms is illustrated schematically in Fig. 2.5.
2.4 Beyond G-Proteins and Application to Therapeutics

At this point in time, there is little doubt that ligands are able to exhibit functional selectivity and the question now becomes, is it physiologically relevant and can pharmacology harness such a potentially powerful mechanism to therapeutic advantage? Some of the earliest work in this area, originating from work closely associated with therapeutics (namely dopamine treatment of CNS disorders; for review see (35)), suggests that direct therapeutic advantages may be derived from functional selectivity. Functional selectivity also has been associated with CNS behavior patterns for serotonin ligands through the 5-HT$_{2A}$ receptor providing further links to the molecular mechanism and therapeutic events (36). For future work in this field, two general ideas may be relevant. The first is that the efficacy of any given ligand is defined by the assay used to detect it, e.g., the ERK stimulating activity of propranolol was not detected for 40 years until propranolol was tested in an ERK assay (37–39). A related idea is that binding of ligands to receptors is an active, not passive, process and that ensembles of receptor conformations are changed by the binding of ligands (i.e., see (40)). Therefore, the most generic
screening assay available may be the most efficient since this would detect all compounds that bind to the receptor with no reference to predefined efficacy. Functional efficacies then could be detected in various other assays on a smaller scale. Thus, a generic screen (i.e., bioluminescence resonance energy transfer (BRET) and fluorescence resonance energy transfer (FRET)) of a million compounds might detect 300 that bind and then these could be tested in 5–10 therapeutically oriented assays to determine possible useful activity (Fig. 2.6). This may be preferable to arbitrarily choosing a therapeutically oriented assay to start with and risk not seeing ligand interaction with molecules that bind to the target but do not elicit that particular observed effect. In this sense, any ligand that binds to the receptor should be considered a potentially efficacious drug in a variety of settings.

**Fig. 2.6** Two modes of screening. In generic screening (i.e., BRET or FRET detection of ligand-receptor interaction), the fact that the ligand-bound receptor is thermodynamically different from the unliganded receptor predicts that all molecules that bind to the receptor will be detected. Secondary testing of the subset of binding molecules (much smaller set than the original library) can then bind compounds with respect to function. On the right is shown a therapeutically relevant screen where a specific receptor coupling pathway is chosen for detection. This may shorten the process if evidence is strong that the pathway is all that is required for therapeutic activity. On the other hand, ligands with unknown potential will be missed and the approach will not work if the chosen pathway is the incorrect one.
It may be useful to speculate on where functional selectivity of natural system might be a useful physiological control. One such area might be in systems with pleiotropic receptor coupling. For example, associations between selective coupling and physiology have been made for the thyrotropin receptor, which couples to Gs and Gq protein; the Gs protein coupling may be associated with thyroid growth and differentiation, while the Gq coupling may be more associated with thyroid hormone synthesis (41). Another case may be the orexin receptor, where selective agonism may have significance with respect to differences in adrenal steroid production and release (Gs protein) and catecholamine release (Gq protein) (42,43).

A second area where functional selectivity may be important is in redundant systems, and it raises the question whether or not natural systems make use of this potentially powerful mechanism. There are suggestions that this may be the case. Thus, studies show that ligand-bound receptor active states (some with natural ligands such as catecholamines, dopamine, and natural enkephalins) differ from spontaneously formed constitutive active states (44–46). This would be a way to achieve fine control of signaling through the same receptor in response to hormonal input vs cellular constitutive setpoints.

Another setting where functional selectivity may be important is systems where the chemical input to the receptor is redundant. Perhaps the most redundant and pleiotropic receptor system of all is the chemokine system, where multiple natural agonists are known to activate a range of receptors (Fig. 2.7). It might be expected that this redundancy could naturally be exploited to yield subtle differences in signaling for physiological benefit. Evidence of such functional selectivity is emerging;

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Fig. 2.7 Redundancy of chemical input to chemokine receptors. Taken from (47)
for example, two natural agonists for the CCR7 chemokine receptor, namely CCL19 and CCL21, differ in the type of pathway stimulation they elicit through this receptor. Specifically, only CCL19, not CCL21, causes the receptor to undergo agonist-dependent phosphorylation and recruitment of β-arrestin as a means of terminating the G-protein stimulus (48).

A therapeutic application of functional selectivity theoretically can be found in the treatment of AIDS through CCR5-mediated blockade of HIV-1 entry. Specifically, a number of allosteric CCR5 HIV-1 entry inhibitors have been described (see 49,50 for review) and these function through prevention of the virus binding to and utilizing CCR5 for infection. Interestingly, separate data indicate that the natural chemokine system can be beneficial in the delay of AIDS from HIV-1 infection (51–56). Although suggestive, these studies are difficult to interpret since measurement of elevated chemokines is technically difficult as chemokines are produced and utilized at the site of action. A novel way around this limitation has been reported in a large clinical trial (1,064 patients) where the gene copy number for a variable chemokine ligand for CCR5 (CCL3L1) is strongly correlated with AIDS survival (57). Specifically, patients with high gene copy numbers for CCL3L1 have a much greater rate of survival and slowed progression to AIDS than patients with a low gene copy number for this chemokine. At present, on the one hand, all clinically tested CCR5 HIV-1 inhibitors block chemokine function as well as HIV-1 entry; theoretically, an allosteric modulator that prevents the utilization of CCR5 by HIV-1 but otherwise allows the natural chemokine system to function through this receptor (i.e., exhibits functional selectivity) could increase the efficacy for treatment of AIDS. On the other hand, it may be simplistic to suggest that preservation of chemokine function could uniformly be beneficial since CCR5 receptor activation through natural chemokines is known to produce a variety of effects, some not conducive to protection against AIDS (Table 2.1). Thus, although activation of AKT and increased neuronal survival in AIDS dementia have been suggested to be useful effects of chemokine receptor stimulation in HIV-infected patients, other signals such as activation of P38 leading to immunocompetent cell death, Gi-protein-mediated increased replication of HIV virus, and nonspecific inflammation have negative ramifications (58–61). This makes it incumbent upon pharmacologists to understand the pathophysiology of the target to define which functions mediated by the receptor would be therapeutically beneficial. One protective action of CCR5 activation that has been identified as beneficial is the internalization of the CCR5 receptor since this would block HIV-1 entry and also preclude viral resistance through mutation (51–56).

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<th>Table 2.1</th>
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<tr>
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<td>• ↑HIV replication</td>
<td>• ↑CCR5 internalization</td>
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<td>• ↑Inflammation</td>
<td>• ↑Neuronal survival (AIDS Dementia)</td>
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Data from (58–61)
2.5 Conclusions and Perspective

The ability of different ligands to direct signals to different cellular interactants to produce texture in signaling (a general phenomenon referred to as “functional selectivity”) is well established in mechanistic, theoretical, thermodynamic, and experimental terms. It would be tempting to believe that such a versatile physiological system would not be redundant in normal biology but rather would be employed for fine control of chemical signaling to cells. However, to date, sound data to associate this pharmacological mechanism with normal physiology or pathophysiology is still lacking. However, this gap should be eliminated in the near future as new classified functional ligands are introduced into clinical therapy; it would be hoped that translational medicine will connect functional selectivity with therapeutic phenotypic behavior. The supply end of this process still requires functionally selective ligands and the key to finding these is the appropriate assay system (both in screening and lead optimization of new chemical entities). At the very least, the concept of receptors as “on-off” switches (as first described by John Newport Langley (1852–1926) – (62)) is laid to rest with the appreciation of the complexity of seven transmembrane signal processing capability.

References


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