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Ligand bias prevents class equality among beta-blockers

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β-Blockers are used for a wide range of diseases from hypertension to glaucoma. In some diseases/conditions all β-blockers are effective, while in others only certain subgroups are therapeutically beneficial. The best-documented example for only a subset of β-blockers showing clinical efficacy is in heart failure, where members of the class have ranged from completely ineffective, to drugs of choice for treating the disease. Similarly, β-blockers were tested in murine asthma models and two pilot clinical studies. A different subset was found to be effective for this clinical indication. These findings call into question the current system of classifying these drugs. To consider 'β-blockers', as a single class is misleading when considering their rigorous pharmacological definition and their appropriate clinical application.

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Introduction

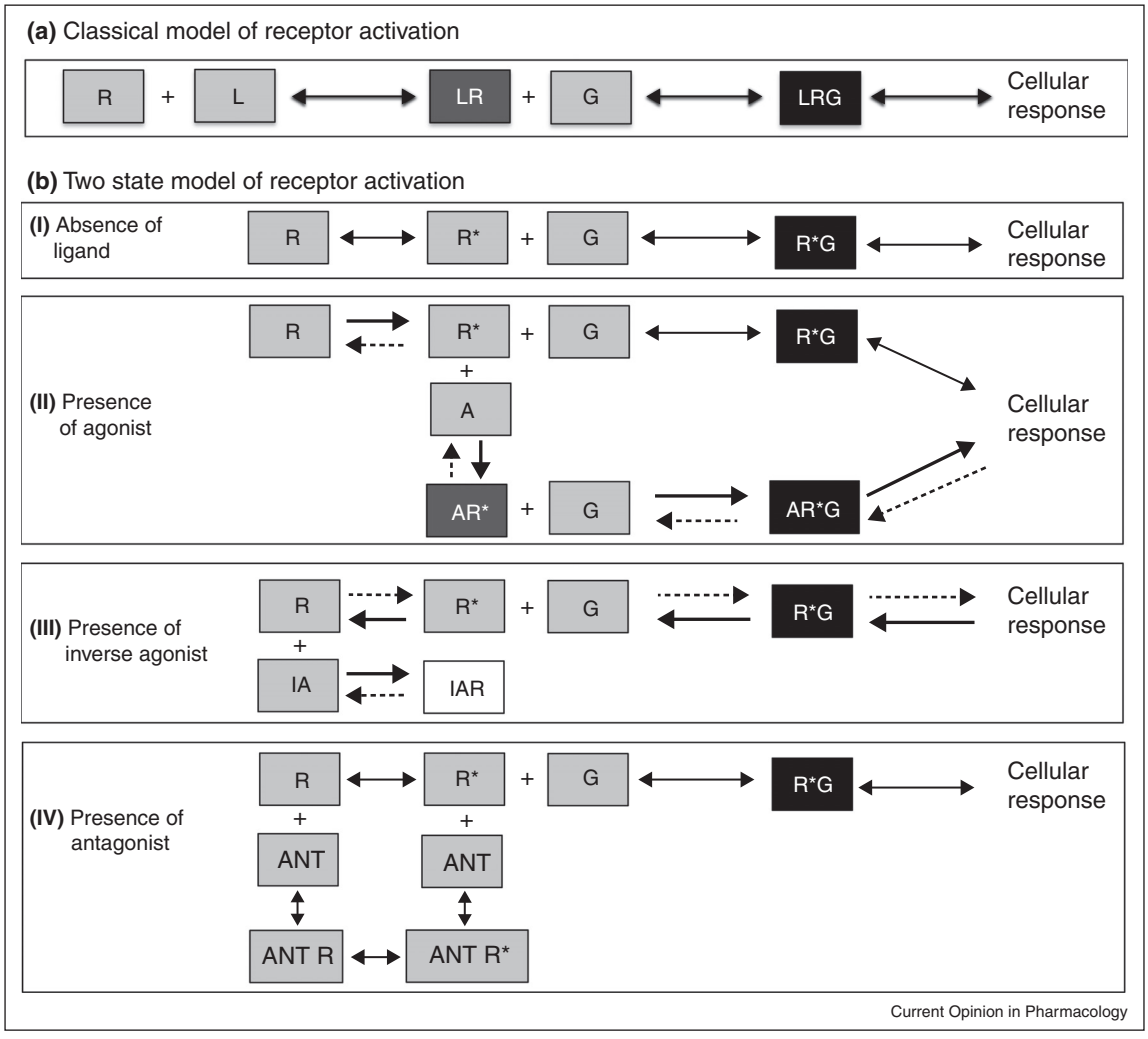
Asthma is a chronic inflammation of the airways characterized by inflammatory cell infiltration of the airways, an increase in mucus production and secretion, and airway hyperresponsiveness (AHR). A variety of different mediators and receptors regulate the development and exacerbation of asthma. Mainstays of asthma therapy are inhaled glucocorticosteroids and β_2-adrenoceptor (β_2AR) agonists. The latter class of drugs comprises the most effective bronchodilators ever discovered, and is first line therapy for rescue during an asthma attack [1]. However, chronic use of long-acting β_2AR agonists has been associated with loss of asthma control in murine and human studies, and a small, but significant increase in mortality in human studies [2–4]. Also, studies in murine models of asthma suggest β_2AR signaling pathways play an essential permissive role in the development of the asthma phenotype. These data include the finding that β_2AR knockout mice have an attenuated asthma phenotype [5], and that administration of 5 different β-blockers, including the selective β_2AR inverse agonist, ICI-118,551, results in an attenuation of the murine asthma phenotype [6,7]. However, administration of some βAR antagonists like alprenolol did not attenuate the asthma phenotype in the same model, and inhibited the beneficial effect of nadolol [5,7]. These results highlight the importance of β_2AR, its signaling profiles and the need to understand its regulation in the development or attenuation of the murine asthma phenotype. This review will explore the pharmacological basis of the different signaling profiles of the various β_2AR ligands, and suggest their roles in asthma therapy. Finally, we will discuss the limitations and practical possibilities of screening desired β_2AR ligands based on a novel holistic cellular label-free impedance assay.

The evolution of receptor theory

Established theory for the activation of G protein-coupled receptors assumes a receptor in an inactive state 'R', which binds to the ligand 'L' and produces a binary complex (LR). If the binary complex has affinity for downstream effectors (like G proteins), the ligand is an agonist and leads to a cellular response (Figure 1a). If ligand binding to the receptor produced a binary complex with no affinity for downstream effectors it is termed an antagonist. With the discovery of constitutively or spontaneously active conformations of receptors, it became necessary to include another conformation of the receptor 'R*' which was capable of signaling in the absence of the ligand 'A' [8].

The two-state model of receptor activation proposes that receptors exist in two conformations, R (the inactive state) and R* (the active state) and both states exist in equilibrium. This two-state model of receptor activation allows the classification of ligands as agonists, antagonists, or inverse agonists, on the basis of their relative affinities for the inactive (R) and the active (R*) receptor conformations [9–13]. As shown in Figure 1b, an agonist (A) has more affinity for the active state, it binds to the R* conformation forming AR* and shifts the equilibrium towards R*. Conversely, an inverse agonist (IA) has more affinity for the inactive conformation R, and forms IAR shifting the equilibrium towards R. This results in a reduction in the constitutive (basal) activity of the system by reducing the number of constitutively active receptors.

Figure 1



(a) Classical model of GPCR activation. Receptor 'R' when activated by a ligand L, forms a binary complex LR, that has high affinity for signaling molecules like G proteins. The LRG complex can activate downstream signaling pathways eliciting cellular responses. Antagonist-bound receptor has low or no affinity for G and prevents downstream signaling. **(b)** Two-state model of receptor theory. I. Receptors can exist in two conformations, the inactive conformation 'R' and the active conformation 'R*'. The active conformation R* has high affinity for G and can form R*G complexes to stimulate cellular responses in the absence of a ligand, referred to as constitutive signaling. These conformations exist in equilibrium in a system until a stimulus disturbs the equilibrium. II. In the presence of an agonist 'A', which has higher affinity for R* than R, the equilibrium shifts towards R*. The binary complex of AR* has higher affinity for G and stimulates downstream signaling. III. In the presence of an inverse agonist 'IA' with higher affinity for the inactive conformation R than R*, the equilibrium shifts towards R once the IAR complex is formed. This further shifts the equilibrium away from R*G and reduces the constitutively active R* cellular response. IV. In the presence of an antagonist with similar affinities for R and R* to form ANT R and ANT R* complexes, the equilibrium is maintained and the constitutive activation of cellular responses by R*G is not affected because the equilibrium does not shift in either direction.

An antagonist has relatively equal affinity for both conformations R and R* and does not alter the equilibrium. An antagonist, sometimes referred to as a 'neutral antagonist' for added emphasis, cannot 'block' or antagonize the constitutive activity like an IA; but antagonists block the effects of both agonists and inverse agonists [9,14–16]. A partial agonist (not shown in figure), has a relatively higher affinity for R* as compared to R, but the differential affinity for R* relative to R is lower than that of a full agonist. Similarly, a partial inverse agonist (not shown in figure) has a relatively higher affinity for R than R* conformation but again with lower differences in the affinity for R relative to R* when compared to a full inverse agonist.

Role of constitutive versus ligand-activated receptor in asthma

Based on the two-state receptor activation theory, β_2AR signaling can result from either a ligand or by the constitutively-active receptor in the absence of a ligand [11].