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EVOLVING CONCEPTS OF DRUG ACTION: AN INTEGRATIVE REVIEW OF DRUG-RECEPTOR INTERACTION MODELS

CONCEITOS EVOLUTIVOS DA AÇÃO DE FÁRMACOS: UMA REVISÃO INTEGRATIVA DOS MODELOS DE INTERAÇÃO FÁRMACO-RECEPTOR

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Abstract

This review synthesized the evolution of the major theoretical models of drug action and drug–receptor interactions, based on searches conducted in PubMed/NCBI, SciELO, and the Virtual Health Library (BVS-BIREME/PAHO/WHO), complemented by authoritative reference works. From Langley's proposal of "receptive substances" and Ehrlich's principle that drugs exert their effects through binding to specific molecular targets, pharmacodynamics has progressively developed quantitative models of drug action. The Law of Mass Action established the reversibility of drug–receptor binding and its dependence on affinity, expressed by the dissociation constant (Kd). Clark's receptor occupancy theory linked pharmacological responses to receptor occupancy; however, subsequent evidence demonstrated that receptor occupancy alone cannot account for the variability of pharmacological effects. Ariëns and Stephenson introduced the concepts of intrinsic activity and efficacy, distinguishing receptor binding from

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receptor activation and providing a framework for understanding full and partial agonists, antagonists, and spare receptors. Subsequent models incorporated receptor conformational flexibility, replacing static paradigms with dynamic approaches. Two-state and multistate models, together with macromolecular perturbation theory, account for constitutive activity, inverse agonism, and biased signaling. Thus, modern pharmacology views drug action as a dynamic process dependent on affinity, efficacy, receptor conformation, and signaling pathways across different cellular contexts.

Keywords: Drug Action, Drug Action Theory, Molecular Mechanisms.

Resumo

Esta revisão sintetizou a evolução dos principais modelos teóricos da ação dos fármacos e das interações fármaco-receptor, com base em buscas no PubMed/NCBI, SciELO e BVS-BIREME/OPAS/OMS, complementadas por obras de referência. Desde a proposta de Langley sobre "substâncias receptivas" e o princípio de Ehrlich, segundo o qual os fármacos atuam mediante ligação a alvos específicos, a farmacodinâmica desenvolveu modelos quantitativos. A Lei da Ação das Massas estabeleceu a reversibilidade da ligação e sua dependência da afinidade, expressa pelo Kd. A teoria da ocupação de Clark relacionou resposta e ocupação de receptores, mas evidências posteriores demonstraram que a ocupação isolada não explica a variabilidade dos efeitos. Ariëns e Stephenson introduziram atividade intrínseca e eficácia, distinguindo ligação de ativação e explicando agonistas totais e parciais, antagonistas e receptores reserva. Modelos posteriores incorporaram a flexibilidade conformacional, substituindo paradigmas estáticos por abordagens dinâmicas. Teorias de dois ou múltiplos estados e da perturbação macromolecular explicam atividade constitutiva, agonismo inverso e sinalização enviesada. Assim, a farmacologia moderna compreende a ação dos fármacos como fenômeno dinâmico, dependente de afinidade, eficácia, conformação e sinalização em diferentes contextos celulares.

Palavras-chave: Ação de Fármacos, Mecanismos Moleculares, Teoria da Ação de Fármacos.

INTRODUCTION

The effects of drugs on the human body remained unknown for a long time and were often interpreted through mystical or supernatural explanations (YU and THAM, 2024). With the advancement of science, new theories were progressively developed and refined, enabling a more detailed understanding of how drugs interact with the molecules and cells of the body (Suvarna, 2011). In this context, hypotheses regarding the mechanisms of drug action have been proposed and improved over time, reflecting the technological progress available in each historical period (Kenakin, 2022).

It is essential to recognize that historical theories and models of drug action can be integrated in a complementary manner, as each has substantially contributed to the development of pharmacology. These frameworks not only elucidate the fundamental principles that govern drug-organism interactions but also provide the conceptual basis for innovation in pharmaceutical research (Deiab et al., 2022). The accumulated knowledge derived from these approaches deepens our understanding of drug mechanisms of action, supports the development of novel therapeutic strategies, and enhances rational drug design and synthesis. Therefore, the continued study and refinement of drug action theories remain indispensable for advancing scientific knowledge and improving the efficacy and safety of therapeutic interventions (Welsch, Snyder and Stockwell, 2010).

In recent decades, among the tools that have contributed to a better understanding of drug action theories, molecular modeling has become particularly prominent. Through computational simulations, it enables the analysis of interactions between molecules and their biological targets, such as receptors and enzymes (Rocha and Sant'anna, 2024). Its application allows the visualization of structure-activity relationships (SAR), facilitating the identification of structural features critical to compound efficacy and the refinement of their pharmacodynamic and pharmacokinetic properties (Adelusi et al., 2022; Ferreira et al., 2015). Moreover, techniques such as molecular docking, molecular dynamics, and quantum chemical calculations support the design of more selective molecules, optimizing therapeutic efficacy and reducing adverse effects (Adelusi et al., 2022; Ferreira et al., 2015; Aloui et al., 2024).

The present article aims to review, in a chronological perspective, the different theories and models proposed to explain drug binding and action at their receptors. The models addressed here correspond primarily to the so-called “classical theories,” which stem from the concepts initially postulated by Clark.

METHODOLOGY

The article aimed to synthesize current knowledge on drug action by examining molecular and cellular mechanisms underlying pharmacological responses. A systematic methodology was adopted using DeCS descriptors, including “drug action theory,” “agonist,” “antagonist,” “receptor,” and “pharmacological effect,” to structure a comprehensive search strategy. Literature was retrieved from LILACS via the Virtual Health Library, SciELO Brazil, PubMed, and the CAPES Journal Portal. The search, conducted between February and July 2025, prioritized recent and high-quality studies relevant to pharmacodynamic concepts. This integrative approach provided a consolidated foundation for understanding how ligand-receptor interactions govern therapeutic and adverse effects across diverse pharmacological contexts. These findings support improved analysis of drug efficacy and safety profiles.

The inclusion criteria for selecting studies were: (i) peer-reviewed scientific articles; (ii) publications from any period, with no date restrictions; and (iii) works that centrally addressed theories of drug action. Conversely, the exclusion criteria were: (i) materials published in non-scientific media, such as blogs or institutional documents lacking academic review; (ii) conference abstracts, given their concise nature and lack of detailed analysis; and (iii) studies that mentioned drug action theories only tangentially without treating them as a primary focus.

The texts included in this review were selected for their historical relevance, scientific impact, and depth of discussion on drug action theories. Priority was given to studies providing robust theoretical foundations and meaningful contributions to the understanding of drug mechanisms. In addition to scientific articles, widely recognized pharmacology textbooks were consulted to incorporate classical

principles and updated pharmacodynamic concepts, ensuring a comprehensive and well-structured integration of theoretical and applied perspectives (Cavalcante and Oliveira, 2020).

RESULTS AND DISCUSSION

THEORIES OF DRUG-RECEPTOR INTERACTIONS

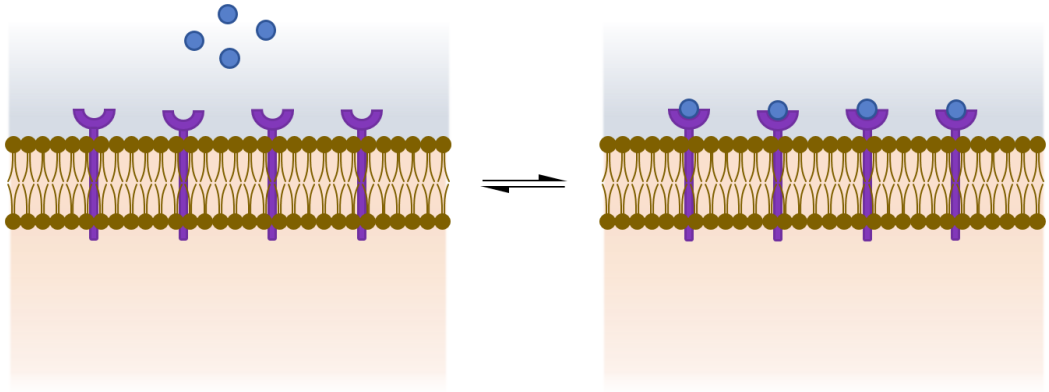
Most drugs exert their effects by binding to specific receptors, a concept originating from Langley's 1905 observations that nicotine-induced muscle contraction was prevented by curare, implying a "receptive substance" responsible for drug action (Maehle, 2004). Ehrlich later strengthened this framework by proposing that pharmacological responses depend on chemical interactions between drugs and defined molecular targets, expressed in his principle that substances act only when bound (Valent et al., 2016). These foundational ideas established modern pharmacodynamics. Subsequent refinements of receptor theory enabled the development of selective agents and more accurate models of drug–receptor interactions, forming conceptual bases that continue to guide contemporary pharmacology (Maehle, 2004; Valent et al., 2016).

Law of Mass Action

The Law of Mass Action states that the rate of a chemical reaction is proportional to the product of the concentrations of the reactants. This principle can be applied to pharmacology, as the interaction between a drug and its receptor follows a similar model, resulting in the formation of a reversible drug–receptor complex (Figure 1) (Aronson and Ferner, 2015).

Figure 1

Drug-receptor reaction according to the Law of Mass Action.



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Starting from the assumption that the binding of one molecule to a receptor does not alter the subsequent interaction of other molecules, and applying the Law of Mass Action, the relationship between the fraction of occupied receptors and the drug concentration can be mathematically described according to Equation 1 (Kenakin, 2015). This relationship is fundamental to the understanding of pharmacodynamics, as it allows the prediction of receptor occupancy at different drug concentrations and aids in determining drug efficacy and potency.

$$\frac{[DR]}{[Rt]} = \frac{[D]}{Kd+[D]} \quad \text{(Equation 1)}$$

Where [D] represents the concentration of free drug; [DR] corresponds to the concentration of drug bound to the receptor; and [Rt] is the total receptor concentration, defined as the sum of occupied and unoccupied receptors. Kd is the dissociation constant, which reflects the affinity of the drug for the receptor, that is, the strength of the ligand-receptor interaction. Higher Kd values indicate lower affinity and weaker binding. This equation demonstrates that the effect of a drug can be increased either by raising the ligand concentration or by increasing the amount of available receptor (Kenakin, 2015).

Occupancy Theory

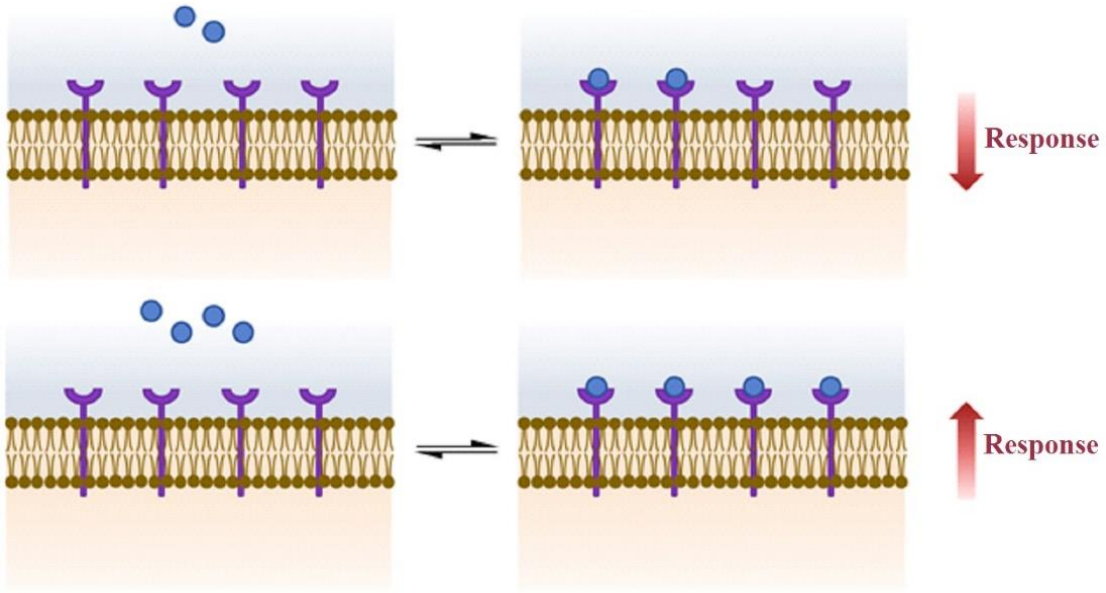
Clark's 1926 receptor occupancy theory provided the first quantitative model of drug-receptor interaction, mathematically relating receptor binding to biological response. The theory posits that pharmacological effect is proportional to the fraction of occupied receptors, with maximal response achieved only upon full receptor saturation (Maehle et al., 2002). Based on the Law of Mass Action, it characterizes association-dissociation equilibria and defines affinity through the dissociation constant (Kd). Thus, drug responses depend on both receptor occupancy and affinity, establishing a foundational framework for modern quantitative pharmacology (Buchwald, 2019; Kenakin, 2015; Calabrese, 2016).

Receptor occupancy theory also assumes that each drug molecule binds independently to a single receptor, without affecting the binding of other molecules. In addition, the fraction of drug bound to receptors is negligible relative to the total amount in solution, ensuring that binding does not significantly alter free drug concentration. Under these conditions, the rate of drug-receptor association is proportional to both drug concentration and receptor availability, providing a quantitative basis for predicting pharmacological responses (Finlay et al., 2020)

According to receptor occupancy theory, 50% receptor binding yields roughly 50% of the maximal biological response, while full receptor saturation is required to achieve the maximal effect. In Clark's original model, this relationship is linear, meaning system activation is directly proportional to the number of occupied receptors (Figure 2) (Buchwald, 2019; Finlay et al., 2020). Although essential to early pharmacodynamic thought, this framework was later refined by models such as receptor activation theory and modified occupancy theory, which incorporate intrinsic efficacy, signal amplification, and the presence of spare receptors (Buchwald, 2019).

Figure 2

Relationship between receptor occupancy and pharmacological response.



Source: Authors, 2026

Although Clark recognized that drug action depends on two factors, drug binding to the receptor and the ability of the drug to elicit a biological effect after binding, his occupancy theory quantified only the first aspect. This limitation represents the principal shortcoming of the model, as it neglects the possibility that different drugs, even when occupying the same proportion of receptors, may elicit distinct biological responses due to differences in their intrinsic efficacies (Berg and Clarke, 2018).

Intrinsic Activity Theory

A refinement of Clark's theory emerged from the studies of Ariëns (1954) and Stephenson (1956). Ariëns observed that not all para-aminobenzoic acid derivatives exhibited biological activity, despite their structural similarity and presumed ability to bind to the same receptor. This finding suggested that receptor binding alone was insufficient to trigger a biological effect. Based on this observation, Ariëns proposed that drug action should be analyzed using two distinct and independent parameters. The first, termed affinity, describes the ability of a drug to bind to its receptor, following the law of mass action as originally defined by Clark. The second parameter, called intrinsic activity, refers to the ability of the drug

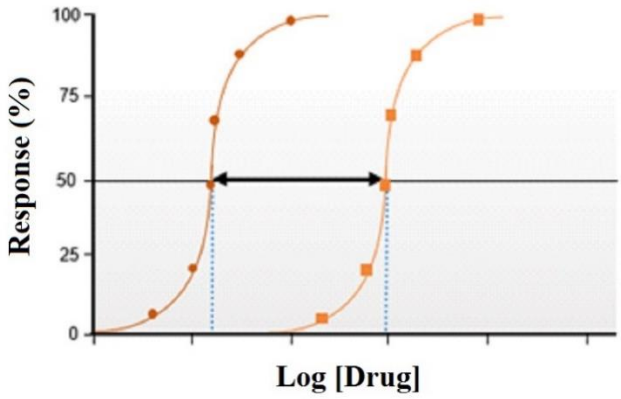
to induce a biological response after binding to the receptor. Thus, while affinity determines the strength of the drug–receptor interaction, intrinsic activity defines the drug's efficacy in generating a cellular effect (Ariëns, 1954). This distinction was fundamental for explaining why some drugs, despite binding to receptors, do not elicit a significant response, and it also enabled the classification of drugs as full agonists, partial agonists, and antagonists, concepts later refined by researchers such as Stephenson.

The concept of intrinsic activity introduced by Ariëns refers specifically to the capacity of a drug not only to bind to its receptor but also to trigger a biological response. This parameter is essential for differentiating among types of agonists because it determines the extent of receptor activation following drug binding. Full agonists possess high intrinsic activity and can elicit a maximal response, mimicking the action of the endogenous ligand. Partial agonists, however, have lower intrinsic activity and cannot produce the maximal response even when occupying all available receptors. Notably, a partial agonist may exhibit receptor affinity equal to or greater than that of a full agonist, yet its efficacy remains limited due to less efficient receptor activation. This clearly demonstrates that pharmacological response depends not only on receptor affinity but also on the drug's capacity to activate the receptor after binding (Mitra, 2009; Whalen, Finkel and Panavelli, 2016).

In this model, a competitive antagonist has high affinity for the receptor but lacks intrinsic activity; that is, it binds to the receptor without activating it. By directly competing with the agonist for the same binding site, the antagonist temporarily prevents agonist-receptor interaction, thereby reducing the agonist's effect. As a result of this competition, the agonist's dose-response curve shifts to the right, indicating that higher concentrations of agonist are required to achieve the same effect. However, because competitive antagonism is reversible, the maximal response of the agonist is not diminished, provided that sufficient agonist is administered to overcome the antagonist. Competitive antagonists do not produce pharmacological effects on their own; nonetheless, in the presence of an agonist, they reduce the magnitude of the agonist's response by hindering its receptor binding (Figure 3) (Wyllie and Chen, 2007).

Figure 3

Shift of the dose-response curve by a reversible competitive antagonist.



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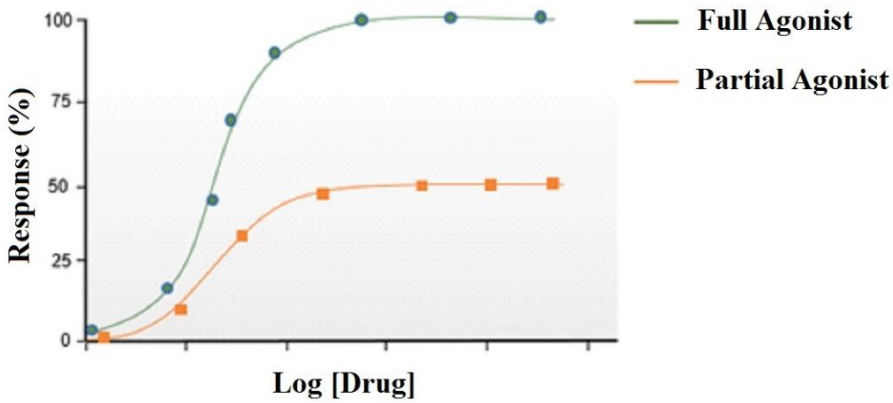
Stephenson further refined the concepts introduced by Ariëns by formally proposing the idea of the *partial agonist*. Unlike a full agonist, which fully activates the receptor and elicits a maximal response, a partial agonist is incapable of producing the maximal effect even when all available receptors are occupied. Moreover, a partial agonist can compete with a full agonist for receptor binding. As its concentration increases, it progressively replaces the full agonist at the receptor, thereby diminishing the overall response. This occurs because, although the partial agonist occupies the receptor, it does not generate the same degree of activation as the full agonist. Consequently, increasing concentrations of a partial agonist can suppress the maximal response to a level determined by its intrinsic efficacy. A drug's intrinsic efficacy is quantified on a scale from 0 to 1, where a full agonist has an intrinsic efficacy of 1, and a partial agonist has a value greater than 0 but less than 1, reflecting its limited capacity to activate the receptor (Figure 4) (Buchwald, 2017; Finlay et al., 2020).

Figure 4

Dose–response curves of partial and full agonists.



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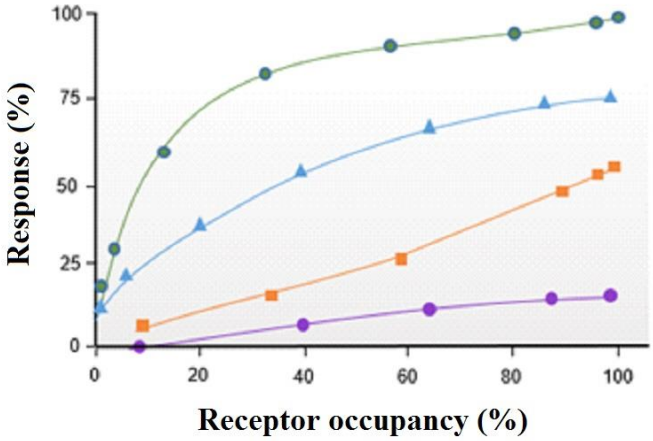
Intrinsic Efficacy Theory

The term intrinsic activity was eventually replaced by efficacy, and its conceptual framework was refined by Stephenson (Stephenson, 1956). Although related, the two terms are not identical. Intrinsic activity, as originally defined, is derived directly from the concentration-response curve and represents the ratio between the maximal effect produced by a test agonist and that produced by a full reference agonist. This interpretation assumes a linear relationship between receptor occupancy and response, an assumption that does not always capture the complexity of receptor activation mechanisms (Buchwald, 2017; Clarke and Bond, 1998).

Efficacy, in contrast, cannot be determined solely from the concentration-response curve. Its calculation requires transforming this curve into a receptor-occupancy-response curve, which evaluates the relationship between the fraction of receptors occupied and the resulting biological response (Figure 5). This theoretical refinement clarified that two drugs may exhibit the same intrinsic activity value of 1, and thus be classified as full agonists, yet still differ in their efficacy due to variations in the efficiency of receptor activation and downstream signal transduction (Buchwald, 2017; Finlay et al., 2020).

Figure 5

Receptor-occupancy–response curves illustrating intrinsic efficacy for a full agonist and partial agonists.



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A major conceptual advance was proposed by Furchgott in 1966, who defined drug efficacy as the product of a ligand's intrinsic activity and the concentration of active receptors within a tissue (Kenakin, 2013). This model showed that efficacy is shaped not only by ligand properties but also by tissue-specific factors such as receptor density, spare receptors, and coupling efficiency between occupancy and response. It improved upon intrinsic activity theory, which considered only ligand characteristics and failed to account for tissue-dependent modulation of pharmacological effects (Kenakin, 2013).

A key conceptual advance was the recognition that maximal tissue response can occur without full receptor occupancy. This was demonstrated by the parallel rightward shift of a full agonist's concentration-response curve after irreversible antagonism, without loss of intrinsic activity, indicating that many receptors must be inactivated before efficacy declines (Kenakin, 2013; Buchwald, 2020).

Nickerson (1956) proposed that some tissues contain excess receptor populations, introducing the concept of spare receptors. Under these conditions, maximal responses can be achieved even when only a small fraction of receptors is occupied, demonstrating that the occupancy-response relationship is not inherently linear (Swillens and Dumont, 1980). Several systems exemplify this phenomenon: activation of the human calcitonin receptor type 2 requires only ~20% occupancy for near-maximal effects; the guinea pig ileum exhibits maximal histamine-induced contraction at ~2% occupancy; and β-adrenergic

stimulation markedly increases cardiac contractility at low receptor occupancy in both rats and humans (Buchwald, 2019).

Receptor-Effector Coupling

When a drug binds to its receptor, conformational changes occur that initiate receptor activation and ultimately generate a pharmacological response. The process linking receptor occupancy to the final effect is known as coupling and may involve van der Waals forces, hydrogen bonding, or, less commonly, covalent interactions (Katzung, 2023). Importantly, the relationship between receptor occupancy and response is not always linear (Swillens and Dumont, 1980). A key determinant of this nonlinearity is the presence of spare receptors, or receptor reserve. Experimentally, this can be demonstrated by administering an irreversible antagonist together with an agonist: even when part of the receptor population is permanently inactivated, a maximal response may still occur because unoccupied receptors remain sufficient for full signaling. However, under these conditions, the agonist's potency is typically reduced (Buchwald, 2020).

As the concentration of the irreversible antagonist increases, it begins to occupy not only the spare receptors but also the receptors required for the agonist to produce its maximal effect. Consequently, the maximal efficacy of the agonist can no longer be achieved (Buchwald, 2017; Buchwald, 2020). This phenomenon has important implications in clinical pharmacology, as it may influence dose selection and the interpretation of drug behavior in the presence of antagonists.

PHARMACODYNAMIC MODELS OF DRUG-RECEPTOR INTERACTIONS

The interaction between a drug and its receptor is one of the key determinants of the pharmacological response. Various pharmacodynamic models have been proposed to explain this interaction, taking into account structural and dynamic features of the drug-receptor complex.

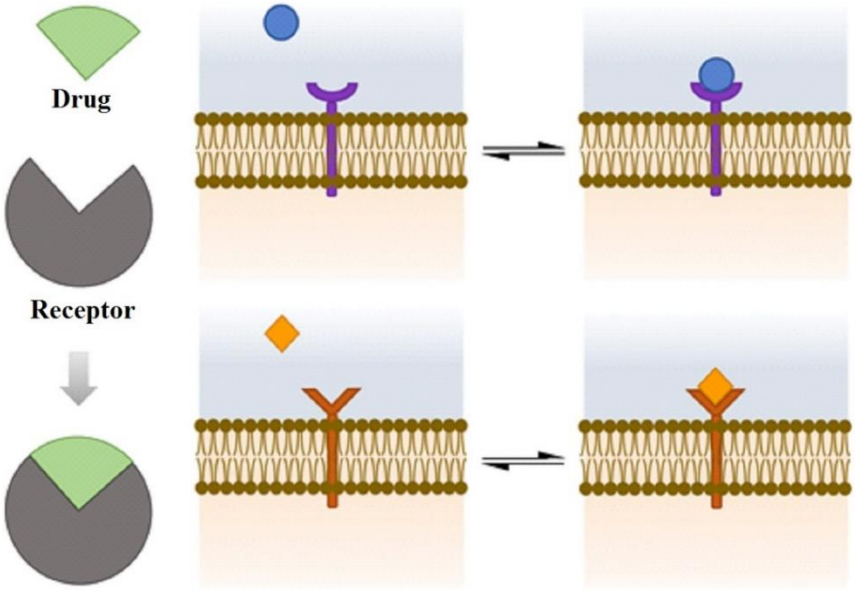
Static Model

One of the earliest explanations for enzyme–substrate recognition was the lock-and-key model (Figure 6), proposed by Emil Fischer in 1894, which described chemical reactions as dependent on a precise spatial fit between an enzyme and its substrate (Fechete, 2016; Verli and Barreiro, 2004). This model assumes rigid structural complementarity, with the ligand fitting the receptor much like a key fits a specific lock. However, its limitations soon became evident. A major criticism is that structurally diverse molecules can interact with the same binding site, as seen with competitive antagonists that compete with endogenous ligands despite lacking close structural similarity, demonstrating that receptor-ligand interactions cannot always be explained by strict geometrical complementarity (Koshland, 1994).

Rigid models of drug–receptor interactions are widely used in pharmacology education because of their didactic clarity and usefulness in introducing fundamental concepts about molecular recognition. However, they provide simplified representations of highly complex processes and may promote misinterpretations or an overly reductionist view of pharmacodynamics (Verli and Barreiro, 2004). In contrast, dynamic models, incorporating receptor conformational flexibility and microenvironmental influences, offer a more accurate and mechanistically coherent framework, consistent with advances in structural biology and medicinal chemistry (Sharma et al., 2024).

Figure 6

Lock-and-key binding model.



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Dynamic Model

In 1964, Belleau introduced the macromolecular perturbation theory, which focuses on qualitative aspects and aids in visualizing the molecular events responsible for biological responses. This theory was fundamental to advancing the understanding of drug-receptor interactions and contributed significantly to the evolution of molecular pharmacology. Belleau proposed that, like enzymes, receptors are protein in nature and undergo conformational changes upon interacting with drugs. He described two main types of conformational perturbation: a) *Specific conformational perturbation* - induced by agonists and associated with the generation of a biological response; and b) *Nonspecific conformational perturbation* - induced by antagonists and not associated with the production of a biological response (Belleau, 1964; De Nucci, 2021).

This model represented a major advance by conceptualizing receptors as flexible structures, thereby influencing the development of new computational approaches for studying drug-receptor interactions. Today, macromolecular perturbation theory is widely applied in methodologies such as 4D-

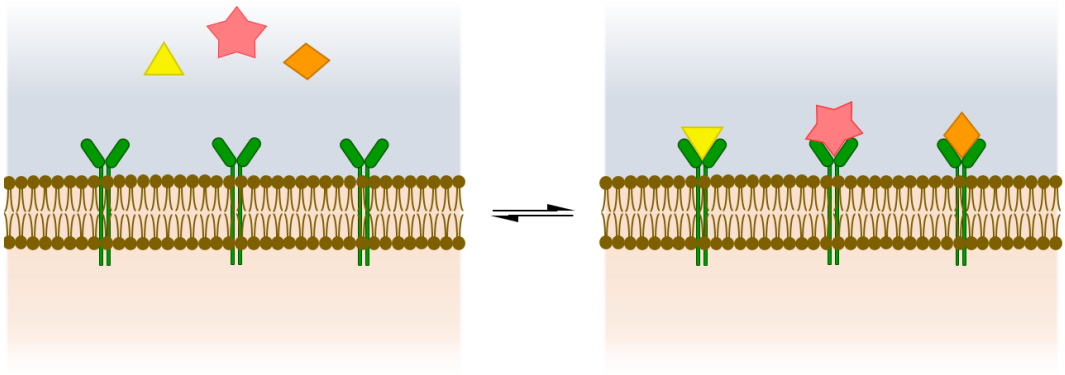
QSAR, flexible docking, molecular dynamics, and Monte Carlo simulations-tools that are essential for modeling and predicting the biological activity of novel compounds (Verli and Barreiro, 2004).

Induced-Fit Model

The induced-fit theory was first proposed by Koshland and collaborators based on enzymatic systems. It suggests that, upon complex formation, the substrate induces a conformational change in the enzyme subunit with which it interacts. This conformational shift may be transmitted to neighboring subunits, driving the enzyme into the conformation required for catalytic activity (Figure 7) (Verli and Barreiro, 2004).

Figure 7

Different ligands binding to a receptor through spatially induced conformational adjustments.



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This model expands the classical lock-and-key concept by describing a more dynamic, multistage interaction. Initially, the drug and receptor interact at a distance, after which both may undergo structural adjustments that promote optimal alignment, strengthen intermolecular forces, and ultimately form a stable complex. Thus, the ligand can induce or select conformational changes in the receptor, while the receptor can recognize multiple ligand conformations, resulting in highly complex spatial adaptations during binding (De Nucci, 2021).

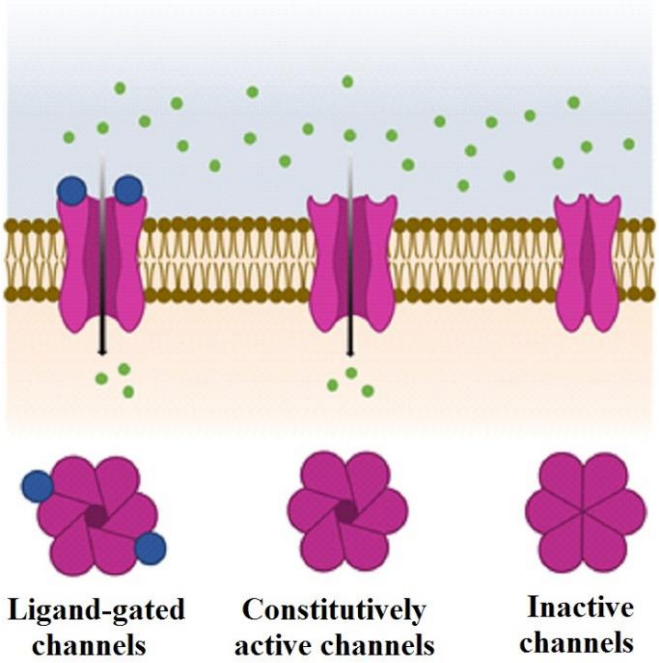
Most drugs bind to multiple receptors, and receptors can interact with different ligands. The induced-adaptation principle proposes that ligand binding can markedly alter receptor conformation, enhancing binding quality and modulating function. Thus, the active site is a dynamic structure capable of structural adjustment to accommodate the ligand (Koshland, 1994). In addition, another way to describe the principle of induced adaptation is to consider that many receptors exist in multiple conformational states, for example, inactive (or closed), active (or open), and desensitized (or inactivated). Drug binding stabilizes one or more of these states, thereby influencing the receptor's overall activity (Golan et al., 2014).

Two-State Theory

This model provides a clear framework for explaining why both agonists and antagonists bind to receptors, yet only agonists elicit activation, while also accounting for constitutive activity (Leff, 1995; Kamepalli et al., 2025). It proposes that receptors transition between resting and active states, with agonists preferentially stabilizing the active state. When constitutive activity is incorporated, receptors may also adopt an active conformation in the absence of ligands. Thus, administered drugs encounter a dynamic equilibrium of receptors distributed across both states. Constitutively active receptors include those for benzodiazepines, histamine, opioids, cannabinoids, dopamine, bradykinin, and adenosine (Leff, 1995; Whalen, Finkel and Panavelli, 2016).

Figure 8

Constitutively active, ligand-activated, and inactive receptor states.

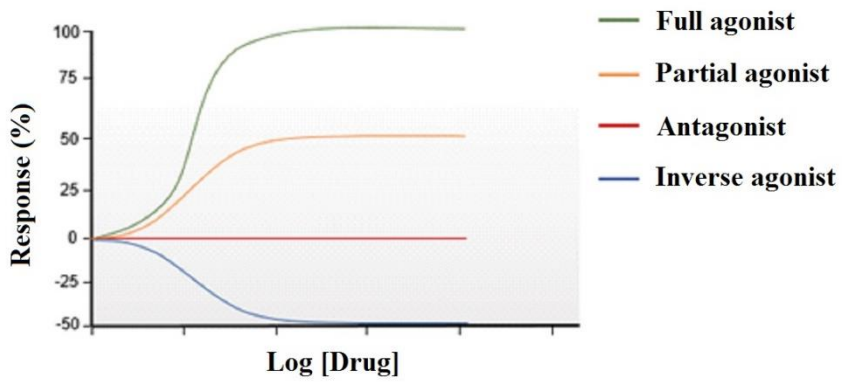


Source: Authors, 2026

According to this model, if a drug exhibits greater affinity for the receptor in its activated state, it will stabilize the receptor in that conformation, shifting the equilibrium toward receptor activation. Such a compound is classified as an agonist. When this preference is strong, a large proportion of receptors are driven into the active state, and the drug is considered a full agonist. Conversely, when the affinity for the active state is only moderate, a smaller fraction of receptors adopts the activated conformation, characterizing the drug as a partial agonist (Leff, 1995; Kamepalli et al., 2025). In addition, a drug may show no particular preference for either the resting or activated state; under these conditions, the equilibrium between the two states remains unchanged, and the compound is classified as a competitive antagonist, exhibiting zero efficacy. Another possibility is preferential binding to the resting state, which shifts the equilibrium toward receptor inactivation and results in negative efficacy (Leff, 1995; Kamepalli et al., 2025). These concepts are illustrated in Figure 9.

Figure 9

Dose-response curves of drugs with different efficacies.



Source: Authors, 2026

This model allows efficacy to be understood as a property determined by a ligand's relative affinity for the two receptor states: resting or activated (LefF, 1995). A practical example of this concept can be observed in the GABAergic system (a central inhibitory system). An agonist depresses the central nervous system, such as benzodiazepines, which induce sleep, sedation, and muscle relaxation, whereas an inverse agonist activates the CNS (e.g., β-carboline), producing convulsant and anxiogenic effects. This model can be broadly applied to explain the functioning of ion channels and clarifies the concept of inverse agonism. However, the two-state model has an important limitation. It is now understood that receptors are not restricted to only two conformations; rather, they possess substantially greater conformational flexibility. Distinct receptor conformations can be stabilized by different ligands, producing diverse functional effects through multiple signaling pathways (Leff, 1995; Kamepalli et al., 2025).

CONCLUSION

This review presents a historical and conceptual synthesis of the principal models proposed to explain drug-receptor interactions. By examining these theories within their historical contexts, it clarifies the scientific and methodological foundations that shaped pharmacology's development. This retrospective approach illustrates how successive advances, often limited by the theoretical and

experimental constraints of their time, progressively contributed to current understanding of drug mechanisms of action.

A consistent theme in this historical trajectory is the inherently multidisciplinary nature of pharmacology. Each theoretical model incorporated contributions from mathematics, chemistry, and biology, including kinetic modeling, molecular structure, intermolecular interactions, and physiological and structural insights. This disciplinary integration highlights the complexity of pharmacodynamic phenomena and shows that major conceptual advances often arose when methodological and theoretical tools from these fields were combined to address questions in receptor research.

It is crucial to recognize that these models are not mutually exclusive; rather, they exhibit a pattern of progressive refinement and conceptual complementarity. Each represented a significant advance within its historical context and often provided the basis for more sophisticated theories. Many remain valuable today, serving not only as pedagogical tools but also as frameworks for rational drug design, interpretation of complex pharmacological data, and elucidation of mechanisms of action for therapeutics whose molecular behavior is not yet fully understood.

Thus, a deeper understanding of this theoretical evolution not only illuminates the trajectory of pharmacology as a scientific discipline but also enhances the capacity to interpret contemporary phenomena, integrate emerging technologies, such as molecular modeling, conformational dynamics, systems pharmacology, and artificial intelligence, and guide future discoveries in the field of drug–receptor interactions.

REFERENCES

Adelusi, T. I. et al. Molecular modeling in drug Discovery. *Informatics in Medicine Unlocked*, London, v. 29, p. 1-18 (100880), 2022.

Aloui, M. et al. QSAR modelling, molecular docking, molecular dynamic and ADMET prediction of pyrrolopyrimidine derivatives as novel Bruton's tyrosine kinase (BTK) inhibitors. *Saudi Pharmaceutical Journal*, London, v. 32, n. 1, p. 1-17 (101911), 2024.

Ariëns, E. J. Affinity and intrinsic activity in the theory of competitive inhibition. I. Problems and theory. *Archives Internationales de Pharmacodynamie et de Therapie,* Ghent, v. 99, n. 1, p. 32-49, 1954.

Aronson, J. K.; Ferner, R. E. The law of mass action and the pharmacological concentration-effect curve: resolving the paradox of apparently non-dose-related adverse drug reactions. *British Journal of Clinical Pharmacology*, Oxford, v. 81, n. 1, p. 56-61, 2015.

Berg, K. A.; Clarke, W. Making sense of pharmacology: inverse agonism and functional selectivity. *International Journal of Neuropsychopharmacology*, Oxford, v. 21, n. 10, p. 962-977, 2018.

Buchwald, P. A three-parameter two-state model of receptor function that incorporates affinity, efficacy, and signal amplification. *Pharmacology Research & Perspectives*, Hoboken, v. 5, n. 3, p. 1-24 (e00311), 2017.

Buchwald, P. A receptor model with binding affinity, activation efficacy, and signal amplification parameters for complex fractional response versus occupancy data. *Frontiers in Pharmacology*, Lausanne, v. 10, p. 1-27 (605), 2019.

Buchwald, P. A single unified model for fitting simple to complex receptor response data. *Scientific Reports*, London, v. 10, p. 1-17 (13386), 2020.

Belleau, B. A molecular theory of drug action based on induced conformational perturbations of receptors. *Journal of Medicinal Chemistry*, Washington, v. 7, n.6, p. 776-784, 1964.

Calabrese, E. J. The emergence of the dose-response concept in biology and medicine. *International Journal of Molecular Sciences*, Basel, v. 17, n. 12, p. 1-14 (2034), 2016.

Cavalcante, L. T. C.; Oliveira, A. A. S. Métodos de revisão bibliográfica nos estudos científicos. *Psicologia em Revista*, Belo Horizonte, v. 26, n. 1, p. 83-102, 2020.

Clarke, W. P.; Bond, R. A. The elusive nature of intrinsic efficacy. *Trends Pharmacological Sciences*, London, v. 19, n. 7, p. 270-276, 1998.

De Nucci, G. *Tratado de Farmacologia Clínica*. 1ª ed., Rio de Janeiro: Guanabara Koogan, 2021. 1248p.

Deiab, G. I. A.; Saadah, L. M.; Basheti, I. A. Using drug chemical structures in the education of pharmacology and clinical therapeutics key concepts. *Brazilian Journal of Pharmaceutical Sciences*, São Paulo, v. 58, p. 1-15 (e21070), 2022.

Fechete, I. Hermann Emil Fischer - The most outstanding chemist in history. *Comptes Rendus Chimie*, Paris, v. 19, p. 1143-149, 2016.

Ferreira, L. G. et al. Molecular docking and structure-based drug design strategies. *Molecules*, Basel, v. 20, n. 7, p. 13384-13421, 2015.

Finlay, D. B.; Duffull, S. B.; Glass, M. 100 years of modelling ligand–receptor binding and response: A focus on GPCRs. *British Journal of Pharmacology*, London, v. 177, n. 7, p. 1472-1484, 2020.

Golan, D. E. et al. *Princípios de Farmacologia*: A base fisiopatológica da farmacologia. 3ª ed., Rio de Janeiro: Guanabara Koogan, 2014. 933p.

Kamepalli, S. et al. Molecular mechanisms of signaling transduction pathways of drug target molecules with recent advancements and future perspectives for successful therapy: a comprehensive and exploratory review. *Beni-Suef University Journal of Basic and Applied Sciences*, Beni Suef, v. 14, p. 1-20 (51), 2025.

Katzung, B. G.; Vanderah, T. W. *Farmacologia Básica e Clínica*. 15ª ed., Rio de Janeiro: Guanabara Koogan, 2023. 1234p.

Kenakin, T. New concepts in pharmacological efficacy at 7TM receptors: IUPHAR Review 2. *British Journal of Pharmacology*, London, v. 168, n. 3, p. 554–575, 2013.

Kenakin, T. The mass action equation in pharmacology. *British Journal of Clinical Pharmacology*, Oxford, v. 81, n. 1, p. 41-51, 2015.

Kenakin, T. P. *A Pharmacology Primer* - Techniques for More Effective and Strategic Drug Discovery. 6th ed., Cambridge: Academic Press, 2022. 502p.

Koshland, D. E. The key-lock theory and the induced fit theory. *Angewandte Chemie International Edition in English*, Weinheim, v. 33, p. 2375-2378, 1994.

Leff, P. The two-state model of receptor activation. *Trends in Pharmacological Sciences*, Amsterdam, v. 16, n. 3, p. 89-97, 1995.

Maehle, A-H.; Prüll, C-R.; Halliwell, R. F. The emergence of the drug receptor theory. *Nature Reviews - Drug Discovery*, London, v. 1, p. 637-641, 2002.

Maehle, A-H. "Receptive Substances": John Newport Langley (1852–1925) and his path to a receptor theory of drug action. *Medical History*, Cambridge, v. 48, n. 2, p. 153–174, 2004.

Mitra, S. P. Drug-receptor interaction: pharmacology, binding and thermodynamics - A review. *Journal of Surface Science and Technology*, Bangalore, v. 25, n. 3-4, p. 103-152, 2009.

Nickerson, M. Receptor occupancy and tissue response. *Nature*, London, v. 178 (4535), p. 697-698, 1956.

Rocha, V. N.; Sant'anna, C. M. R. From origin to current methods: An overview of molecular modeling applied to medicinal chemistry in the last 30 years. *Journal of the Brazilian Chemical Society*, São Paulo, v. 35, n. 10, p. 1-16 (e-20240103), 2024.

Sharma, G.; Bajaj, P.; Rani, A. A review of drug-receptor interactions in biological systems. *Journal of Emerging Technologies and Innovative Research*, Ahmedabad, v. 11, n. 8, p. e887-e894, 2024.

Stephenson, R. P. A modification of receptor theory. *British Journal Pharmacology*, London, v. 11, n. 4, p. 379-393, 1956.

Suvarna, B. S. Drug - Receptor Interactions. *Kathmandu University Medical Journal*, Kathmandu, v. 9, n. 3, p. 203-207, 2011.

Swillens, S.; Dumont, J. E. Non-linear coupling between receptor occupancy and biologic effect as a requirement for a higher drug efficacy. *Molecular and Cellular Endocrinology*, Amsterdam, v. 20, n. 3, p. 233-342, 1980.

Valent, P. et al. Paul Ehrlich (1854-1915) and his contributions to the foundation and birth of translational medicine. *Journal of Innate Immunity*, Basel, v. 8, n. 2, p.111–120, 2016.

Verli, H.; Barreiro, E. J. Um paradigma da química medicinal: A flexibilidade dos ligantes e receptores. *Química Nova*, São Paulo, v. 28, n. 1, p. 95-102, 2005.

Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. Privileged scaffolds for library design and drug discovery. *Current Opinion in Chemical Biology*, Amsterdam, v. 14, n. 3, p. 347-61, 2010.

Whalen, K.; Finkel, R.; Pavanelil, T. A. *Farmacologia Ilustrada*. 6ª ed., Editora Artmed: São Paulo, 2016. 670p.

Wyllie, D. J. A.; Chen, P. E. Taking the time to study competitive antagonism. *British Journal of Pharmacology*, London, v. 150, n. 5, p. 541–551, 2007.

Yu, C. X.; Tham, C. L. Drug discovery and development: A historical overview, current challenges and perspectives. *Life Sciences, Medicine and Biomedicine*, Kuala Lumpur, v. 8, n. 1, p. 1-11 (137), 2024.