



Defining pharmacological terms based on receptor ligand interactions

Definiendo términos farmacológicos basados en las interacciones ligando receptor

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ABSTRACT

There are several theories of how a drug interacts with a receptor. This review discusses the theories considered the most relevant to elucidate the mechanisms that govern drug-receptor interactions such as the occupational theory proposed by A. J. Clark, who established that drug-receptor interactions can be interpreted as processes that obey the laws of physics and chemistry, proposing for the first time a mathematical approach describing the behavior of a ligand-receptor interaction. This theory has been modified with the development of new techniques, such as recombinant technology, protein crystallization and in silico methodologies, which all contribute with important experimental data for a better understanding of ligand-receptor interaction. Over time the drug-receptor interactions theories became more complex and accurate, and gain a few fundamental parameters such as potency, efficacy, dose, types of agonism (partial, total, inverse), antagonism (competitive and non-competitive) or modulation. The deep understanding of these new concepts in drug-receptor pharmacology, can make the difference between success or failure in pharmacological treatment in the clinical area.

RESUMEN

Existen varias teorías sobre cómo un fármaco interactúa con un receptor. Esta revisión muestra las teorías que se consideran más relevantes para dilucidar los mecanismos que rigen las interacciones fármaco-receptor, como la propuesta por A.J. Clark, quien establece que las interacciones fármaco-receptor pueden interpretarse como procesos que obedecen las leyes de la física y la química, y establece por primera vez un enfoque matemático que describe el comportamiento de una interacción ligando-receptor; este modelo se conoce como teoría ocupacional. Sin embargo, esta teoría se ha modificado con el desarrollo de nuevas tecnologías, como la tecnología recombinante, la cristalización de proteínas y las metodologías in silico, que contribuyen con importantes datos experimentales para comprender la interacción ligando-receptor. De esta manera, las teorías de interacciones fármaco-receptor se volvieron más complejas, precisas y obtuvieron algunos parámetros fundamentales como potencia, eficacia, dosis, tipos de agonismo (parcial, total, inverso), antagonismo (competitivo y no competitivo) o modulación. Es por esto que la implementación de estos nuevos conceptos en la farmacología de las teorías fármaco-receptor en el área clínica puede marcar la diferencia entre el éxito o el fracaso en el tratamiento farmacológico.

INTRODUCTION

In medicine it is common to assume that the majority of medications induce their pharmacological effect(s) through interaction with protein structures called receptors «a beta blocker is administered to decrease the function of beta receptors» however, what is behind these interactions or how they develop? Or how a molecule is able to block the activity of a receptor? Is not always clear for everyone. On this regard, to understand the

mechanisms involved in the drug-receptor interactions, we must first know the models that described these phenomena, although in this review we will not describe the mathematical base of the models, it is necessary to point out that they are essential to fully understand them.

There are several theories describing how a drug interacts with a receptor however, in this short review we will discuss only those considered the most relevant to elucidate. In an introductory manner, the mechanisms

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behind drug-receptor interactions were described first by the occupational theory and the two-state theory. There are other models that further describe parameters to consider before choosing one medication over another to induce a specific response, examples of these models are; the Operational model that describes the necessary intrinsic properties of a molecule allowing its actions on receptors in a tissue-specific manner and at the same time contemplates the molecule velocities of association and dissociation from a receptor¹ and the ternary complex model, useful when describing the interactions of drugs with G coupled protein receptors, where in addition of the inactive and active state of the receptor (this model will be described later), whether or not G protein is bound to the receptor influences the interaction, thus adding more complex states.²⁻⁴

THEORIES OF DRUG RECEPTOR INTERACTION

Paul Ehrlich with his salvarsan and the Magic Bullet, was the first to discuss possible structures capable of interacting with drugs naming them receptors. In 1933 AJ Clark⁵ established that drug-receptor interactions could be interpreted as processes that follow the known laws of physics and chemistry and with this, for the first time, a mathematical approach describing the behavior of a receptor's occupation by a drug was made, this model is known as the Occupational Theory and he postulated that the pharmacological effect of a substance is directly proportional to the number of cellular receptors occupied by the substance.⁶ A representation of this model is shown in [Figure 1](#).

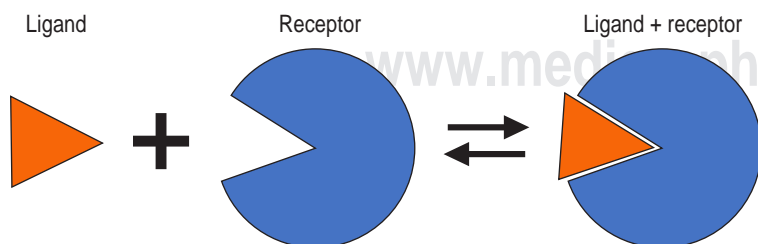


Figure 1: Graphical representation of the occupational theory.

Afterwards Clark clarified some limitations that this model had, in his words. «The application of these formulae to biological data involves certain assumptions which are unproven. In the first place the formulae assume that the receptors in a cell resemble the surface of a polished metal, in that they are all equally accessible to the drug. In the second place the interpretation assumes that the amount of biological effect produced is directly proportional to the number of specific receptors occupied by the drug».⁵

This idea was modified when molecular techniques including recombinant technologies, protein crystallization and computational methodologies (such as molecular modeling and docking) were available. Consequently, the understanding of how a drug is capable of interacting with a receptor is getting more and much closer to what actually really happens.

Other proposed theory suggest that receptors can exist in several states, experiencing different conformational changes and therefore inducing different responses, this theory is called Two-state Receptor Theory. This model emerged from the studies conducted on ion channels, they are observed in two state possibilities or variants, open or closed channel.⁷ Therefore, it was assumed that any other type of receptor could have also two states, active and inactive ([Figure 2](#)).

In this theory, the receptor adopts two possible conformational states that coexist dynamically changing from an active to an inactive state (and viceversa). Therefore, the drug capable to bind to a receptor showing two possible activation states, must have affinity for one of these states. There are known drugs that can bind to the inactive state of the receptor, these drugs are called inverse agonists (this idea will be discussed later), examples are: carvedilol and propranolol, when they interact with specific receptors, they do not only block the inotropic effect induced by natural agonists, but they also lower the inotropism baseline ([Figure 3](#)).⁸

Taking as example drugs used to control arterial hypertension, there are many parameters that influence the binding of a drug to a receptor that are associated with the ligand's properties and structure. Although there are several pathways implicated in the develop-

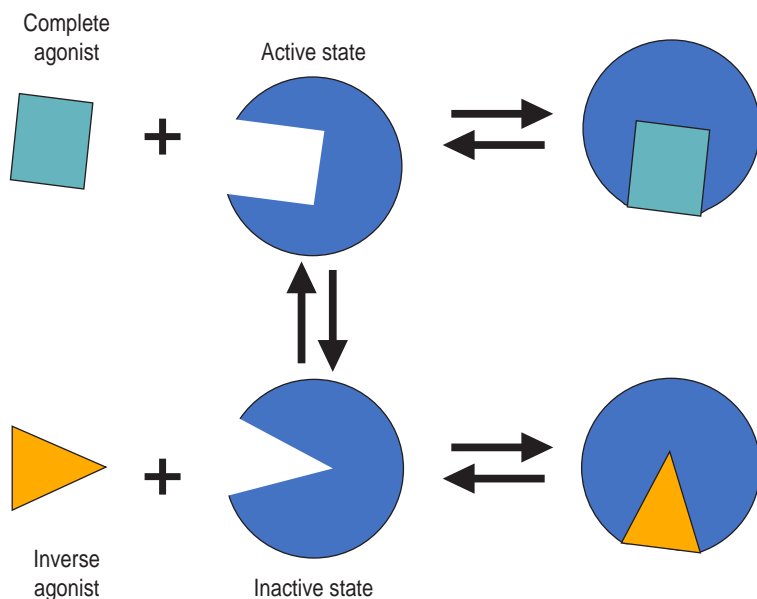


Figure 2: Graphical representation of the **two-state receptor theory**; here is shown the concept of partial and complete agonist that will be discussed later.

ment of arterial hypertension, its treatment involves the use of antihypertensive drugs. The modulation of the activity of alpha and beta adrenergic receptors has been the main target of antihypertensive therapy; due to its direct effect over the peripheral resistance (acting on vascular smooth muscle or interfering with the activity of the systems that inhibits vasoconstriction) or over the cardiac output (with a negative inotropic effect or lowering the ventricular filling pressure) and the renin release.

On this regard, drugs acting on the beta-adrenergic receptor (β AR), i.e. at the β_1 isoform, are the recommended first-line therapy for the management of hypertension in younger patients and in patients with coronary artery disease comorbidities. β AR is activated endogenously, by epinephrine, this molecule is a full agonist of this receptor, because it is able to bind to the receptor, inducing conformational modifications and triggering an effect, in this case, an increase in the cardiac output. Based on these effects and taking in consideration the Occupancy Theory, those designed drugs having effects similar to the induced by the endogenous agonist are also called agonist.

In general, agonists may act interacting in the same site reached by the endogenous ligand

at the receptor (orthosteric site). A common example of a molecule that binds to β_2 receptor is isoproterenol (full agonist), this drug can increase cardiac rate and myocardial contractility (positive chronotropic and inotropic effects) (Figure 3). Interestingly, some drugs are capable to bind at the same site as the agonist, but the action that they trigger is a «submaximal» action, in other words, they do not induce the maximum effect compared with the normal or natural agonist, this type of drugs are called partial agonist, examples are formoterol or albuterol (Figure 3).

From a molecular point of view, three categories of agonist are known: 1) full agonist, triggers the maximum possible effect, occupying the minimum number of available receptors; 2) agonist, triggers the same effect but occupying more receptors compared to the full agonist and 3) partial agonist, triggers an effect, but do not reach the maximum effect despite occupying the same number of receptors as an agonist.

On the other hand, in order to ameliorate the effects produced by agonists of the β_2 AR antagonist drugs are used. Antagonists are drugs that bind to the same receptor as an agonist, but they do not activate the receptor and have no efficacy. An example of this type of drugs is alprenolol (Figure 3), this molecule after binding β_2 AR inhibits the production of renin, thereby inhibiting angiotensin II and aldosterone production and therefore inhibiting their vasoconstriction and water retention effects.⁹

Antagonists are classified depending on their binding site in the receptor, i.e. same site for agonist binding or not. When the antagonist shares the orthosteric site with the agonist, it is called competitive antagonist (bounds easy to break). Since bound antagonists can be removed from the orthosteric site by increasing the concentration of the agonist, i.e. agonist and antagonist compete for the same site (reversible antagonism).

Some antagonists bind covalently (bounds not easy to break) in the binding (orthosteric) site or modify structurally the orthosteric site leading to an impossibility to be displaced by the agonist, when this interaction occurs, the antagonist is called irreversible.

Conversely, when the antagonist binds to an allosteric site (a different site on the receptor

that is able to modulate receptor activity), the interaction is called non-competitive antagonist. In this case, there are two possibilities, 1) the agonist cannot bind into the receptor orthosteric site (because this site changes) or 2) it does bind in it, but the effect is partially or totally annulated even when the agonist concentration is increased.

The drugs classifications described above were the base of therapeutics, however, when the G protein coupled receptors (GPCRs) were discovered the scenario turned more complicated. GPCRs have basal or intrinsic activity; the activation of heterotrimeric G-proteins by receptors involves an equilibrium between conformational states (active and inactive). These states do not need agonist binding (two-state receptor theory). This is even more complicated to understand. Some drugs that were originally classified as antagonists now are classified as inverse agonists, because they favour the possibility of the receptor to adopting an inactive conformation and by this reducing the intrinsic or basal activity of the receptor.

It is clear that the study of the drug-receptor interactions is a process that is continuously evolving, as example, the effects of inverse

agonists on β_2 receptor (a family of GPCRs) - is mediated by «non canonical» or «classic» molecular pathways, that involve the participation of β -arrestin proteins leading to cardioprotective effects. Nadolol and propranolol are examples of these kind of drugs.

New approaches exploring the ligand/receptor interactions have been developed recently. On this regard and based on the fact that there are two possible pathways that can be activated after an agonist binds to its receptor, the concept and creation of the term «biased agonist» is a trending topic in actual pharmacological research. Biased agonists activate selectively one of the two possible pathways, leading to a selective effect depending on the microsite reached by this type of agonist inside the pocket or active site in the receptor. Several studies have suggested that β -arrestin-biased signaling at the β -adrenoceptor induce cardioprotection, leading to the hypothesis suggesting that β -arrestin-biased agonism at the β AR may be a novel therapeutic target for heart failure and/or other cardiovascular diseases. The most representative drug of this group and also the most used drug, is carvedilol. This proposal suggests that the unique efficacy of carvedilol in the treatment of heart failure may be related to the activation of β -arrestin signaling. In addition, carvedilol has other independent of the activation of β AR effects, like relaxation of smooth muscle in vasculature, leading to reduced peripheral vascular resistance and an overall reduction in blood pressure. At higher doses it has also calcium channel blocking and antioxidant capacities. Following the carvedilol example, science is making an effort to find new molecules that can act as biased compounds, leading to better and specific therapeutic results.^{10,11}

CONCLUSION

Based on the information described, the knowledge of the interactions and affinity between a drug and a receptor in its different states becomes relevant. Highlighting the importance of knowing parameters such as potency, efficacy, dosage and types of agonism (partial, full, inverse), antagonism (competitive and noncompetitive) or allosteric modulator.

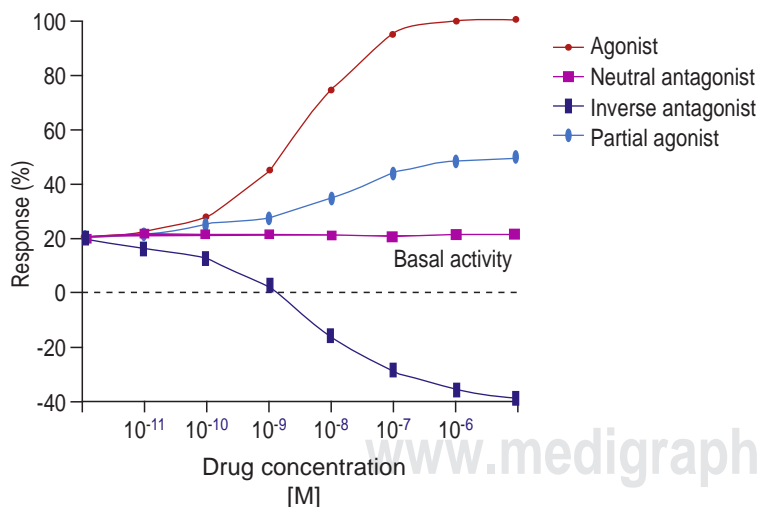


Figure 3: Dose-response curve based on their activity in the beta-adrenergic receptor. Agonist: isoproterenol and epinephrine. Partial agonist: formoterol. Neutral antagonist: alprenolol. Inverse antagonist: propranolol and carvedilol (Modified from: Ferguson SSG, Feldman RD. β -Adrenoceptors as molecular targets in the treatment of hypertension. Can J Cardiol [Internet]. 2014; 30 (5): S3-S8).¹²

The pharmacological approach to explain the action of drugs together with what is learned during clinical practice, can make the difference between success or failure in therapeutics.

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