26. Affinity vs. potency and their constants (K_d and K_i) vs. parameters (EC_{50} and IC_{50})

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What better than the log dose-response curve could characterize pharmacology as a discipline? And in the case of a drug, what could be considered its pharmacodynamic business card? If you thought of efficacy (or should we say intrinsic efficacy?) and potency (or should we say affinity?), you got it right.

Since the concept of efficacy has already been addressed in entry 4 of this glossary, we will devote this entry to the concepts of affinity and potency, and to the constants or parameters that quantitatively characterize them.

Affinity (K_d and K_i constants)

The affinity of a drug for its receptor determines the stability of the drug-receptor complex: the higher the affinity, the more stable the complex. A simple and direct way to measure a drug's affinity for its receptor is through a saturation binding experiment using the labeled drug (radioactively, for example). Generally, the **equilibrium dissociation constant* (K_d)** is calculated, which represents the inverse of the association constant (K_a) and is therefore inversely proportional to affinity (the lower the K_d, the higher the affinity). Although this may seem somewhat counterintuitive, one simply has to remember that K_d represents the molar concentration of the drug sufficient to occupy 50% of its receptors; therefore, the lower this concentration, the greater the affinity of the interaction. K_d can also be defined, and calculated, as the ratio between the dissociation rate constant (k_{-1}) and the association rate constant (k_{+1}), that is: $K_d = k_{-1} / k_{+1}$.

In most cases, researchers do not have access to the labeled form of the drug of interest, and can therefore obtain the K_d value indirectly in a type of assay called a competition experiment, in which its value is derived from the **IC_{50} parameter** (see below). In this context, the value is referred to as K_i, to indicate how it was obtained (the "i" coming from "indirect" or "inhibition" since in this assay the drug of interest competes with/inhibits the binding of a standard radiolabeled drug).

NB. The equilibrium dissociation constant of a reversible competitive antagonist, when determined through a functional assay, is represented by the symbol K_b.

NB. Thanks to the extremely comprehensive structural information obtained through X-ray crystallography, it is possible to estimate the affinity (relative and

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**In an (exaggeratedly) simplified way, we can consider that a constant is a quantity that has the same value in all situations, whereas a parameter is a quantity whose constancy depends on the particular situation; that is, under different experimental conditions a parameter may take on different values.*

sometimes absolute) of different substances for a receptor using molecular modeling techniques such as docking.

Through binding assays, *a priori*, it is not possible to distinguish between agonists, partial agonists, and antagonists, since we measure only the binding of the drug to the receptor. Despite this initial belief, more sophisticated "functional binding" protocols were developed to distinguish agonists from antagonists in G protein-coupled receptors. Although much less common than for GPCRs, we can cite at least one classic case of functional binding for an ionotropic receptor. Ultimately, functional binding assays rely on the fact that receptors can adopt a large number of different conformational states, either due to their entropies or due to allosteric effects resulting from direct interactions with other entities such as signal-transduction proteins (e.g., G protein), membrane phospholipids, or even ions. Drugs that possess some degree of intrinsic efficacy (agonists and inverse agonists) are expected to exhibit different affinities for these various conformational receptor states, whereas drugs "devoid" of intrinsic efficacy (the so-called antagonists) will interact with similar affinities with their receptors across their different conformational states.

Potency (EC_{50} or ED_{50} and IC_{50})

In a functional assay, what we measure is the **potency** of the drug through the **EC_{50}**, **ED_{50}** (if it is an *in vivo* assay where the administered dose is expressed), or **IC_{50} parameter**; these are parameters, and as such, there is no reason to expect them to be similar when determined under different experimental conditions.

EC_{50}, or mean effective concentration, is the concentration of the agonist that produces 50% of its maximal response, whether this effect is stimulatory or inhibitory. This concentration that produces 50% of the maximal response depends not only on the affinity of the drug for the receptor but also on its intrinsic efficacy and on characteristics of the biological system (presence of spare receptors, active mechanisms of agonist removal, or barriers to drug accessibility, for example, in the case of intracellular receptors). Thus, EC_{50} is a descriptive parameter rather than a constant, which is very clear in the case of a drug with high intrinsic efficacy (the so-called full agonist), which displays an EC_{50} value far lower than its K_d when acting in a biological system with a large number of spare receptors. In the case of drugs with low intrinsic efficacy (the so-called partial agonists), the difference between EC_{50} and K_d is much smaller, or even nonexistent.

NB. When the response is a decrease rather than an increase in a function, some authors alternatively use the parameter IC_{50}, although this is discouraged by IUPHAR, which considers that in such cases we are dealing with an inhibitory agonistic effect (Neubig et al., 2003). We agree with this IUPHAR recommendation, even if one must concede that the practice of using the term IC_{50} in this context is very common in the literature and, in our view, should not be considered "incorrect".

NB. Sometimes it may be preferable to express the activity of a drug in terms of the concentration that produces a change from an empirically defined baseline (for example, a 20-mm Hg change in perfusion pressure). If the ECx terminology is used in this context, the appropriate units should be included (e.g., EC_{20mm}) to avoid confusion with EC_{20} (the concentration that produces 20% of the drug's maximal effect).

IC_{50}, or mean inhibitory concentration, is the concentration of a receptor antagonist, an enzyme inhibitor, or a ligand (in a competition-binding assay) that reduces the agonist response, the enzymatic activity, or radioligand binding, respectively, by 50%. Note that IC_{50} values are influenced by experimental conditions (such as the concentration and identity of the agonist, substrate, or radioligand), making it necessary to apply a correction in order to obtain the inhibition constant ($\boldsymbol{K_i}$).

References

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