

Quantitative Pharmacodynamics and Receptor Occupancy, Hill-Langmuir & Antagonism Models — Clinical Treatise 2015

Por Cristiano Ricardo · Publicado em 25/03/2015

University clinical pharmacology treatise by Prof. Cristiano Ricardo on quantitative pharmacodynamics: receptor occupancy, hill-langmuir & antagonism models (Molecular Pharmacology & Receptor Kinetics), featuring mathematical PK/PD modeling, clinical cases, and colorful schematics.

Versão online e eventuais atualizações:

<https://cristianorichardo.com/post/quantitative-pharmacodynamics-receptor-occupancy-hill-langmuir-antagonism-models-2015-03-25>

Molecular Pharmacology & Receptor Kinetics · Clinical Pharmacology & Pharmacotherapy

The magnitude of a pharmacological response reflects a dynamic equilibrium between ligand concentration, receptor occupancy, and intracellular intrinsic efficacy.

Pharmacological Mechanism & Kinetic Schema

Full Agonist ($E_{max} = 100\%$)

Competitive Antag. (Rightward Shift)

Non-Competitive / Irreversible (E_{max} Depression)

$\log [\text{Ligand}] \text{ (M)}$

Response (% E_{max})

The Classical Occupancy Theory vs Modern Operational Models

AJ Clark's classical occupancy model postulated that response is directly proportional to the fraction of occupied receptors. Stephenson and Furchgott revised this to introduce intrinsic efficacy (e) and receptor reserve (spare receptors): in systems with high receptor density, a full agonist can elicit a maximal tissue response (E_{max}) while occupying less than 5% of available receptors.

Competitive Antagonism and the Gaddum-Schild Equation

A reversible competitive antagonist binds mutually exclusively to the orthosteric binding pocket. The concentration-response curve shifts parallel to the right without reducing E_{max} . The magnitude of this shift is governed by the Schild equation: $\log(CR - 1) = \log[B] - \log(K_b)$, where CR is the concentration ratio and K_b is the antagonist dissociation

equilibrium constant.

Non-Competitive, Allosteric, and Irreversible Inactivation

Allosteric modulators and irreversible covalent antagonists (such as phenoxybenzamine at alpha-adrenoceptors) decrease the pool of functional receptors. Once the receptor reserve is completely exhausted, progressive insurmountable depression of maximal efficacy (E_{max}) occurs.

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