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Mechanistic ligand-receptor interaction model: operational model of agonism

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This tutorial explains the basic principles of mechanistic ligand-receptor interaction model, which is an operational model of agonism. A growing number of agonist drugs, especially immune oncology drugs, is currently being developed. In this tutorial, time-dependent ordinary differential equation for simple E_{max} operational model of agonism was derived step by step. The differential equation could be applied in a pharmacodynamic modeling software, such as NONMEM, for use in non-steady state experiments, in which experimental data are generated while the interaction between ligand and receptor changes over time. Making the most of the non-steady state experimental data would simplify the experimental processes, and furthermore allow us to identify more detailed kinetics of a potential drug. The operational model of agonism could be useful to predict the optimal dose for agonistic drugs from *in vitro* and *in vivo* animal pharmacology experiments at the very early phase of drug development.

TUTORIAL

Introduction

In 2006, six healthy volunteers in the UK who participated in a phase 1 study on TGN1412, a humanized CD28 agonist, had severe multiorgan failure.[1] Because of this disaster, we recognized that a more appropriate approach to estimate the optimal initial dosing level is needed especially for drugs with agonistic mechanism.

The following is a scientific background about ligand receptor binding. Clark first introduced the drug-receptor binding concept in 1926 and his occupancy theory was elaborated during the mid of 20th century.[2] Ligand-receptor binding kinetics is essential for the understanding of the drug. For example, the half-life of drug response could be independent of the pharmacokinetic half-life of the drug, if the dissociation rate constant (K_{dissoc}) of the drug from the receptor is small, which means that the drug bound to receptor dissociates slowly. However, it is known that the relationship between percentage of occupied receptor by the drug and effect is not usually linear *in vivo*, that is, the equilibrium dissociation rate constant (K_D) and EC_{50} (drug concentration at the half-maximum effect) is different. To describe the discrepancies, an operational model of agonism was established by Black and Leff.[3,4] The unique characteristic of the operational model of agonism is the 'transducer function' which converts receptor occupation into pharmacological effect. Among all pharmacodynamics models, the E_{max} model has the most robust theoretical base in ligand-receptor binding, according to the law of mass action.[2] However, some drugs, such as the superagonist TGN1412, might exert its maximum effect at lower concentrations at which the receptors were not fully occupied.

In this tutorial, we mathematically derived operational model of agonism for simple ligand-receptor interaction model, which is essential for the understanding. Furthermore, we derived time-dependent ordinary differential equations for simple ligand-receptor interaction model, and operational model of agonism, which is potentially applicable in many *in vitro* and *in vivo* experiments to characterize and predict the response of a novel agonist at the very early stage of development.

Reviewer
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Ligand-receptor interaction model

L and R are ligand and receptor, respectively:

$$[L] + [R] = [LR] \quad (1)$$

Assuming that the response is proportional to the ligand-receptor complex (LR), the amount or concentration of LR over

time is our main interest.

By mass-balance law,

$$\frac{dLR}{dt} = K_{assoc} \times [L] \times [R] - K_{dissoc} \times [LR] \quad (2)$$

$$[R_T] = [R] + [LR] \ (R_T: amount\ of\ total\ receptor) \quad (3)$$

$$\frac{dLR}{dt} = K_{assoc} \times [L] \times ([R_T] - [LR]) - K_{dissoc} \times [LR] \quad (4)$$

The above equations can be rearranged as follows.

$$\frac{dLR}{dt} = K_{assoc} \times [L] \times [R_T] - (K_{assoc} \times [L] + K_{dissoc}) \times [LR] \quad (5)$$

At equilibrium, $\frac{dLR}{dt}$ =0 in the equation 2,

$$[LR] = \frac{K_{assoc}}{K_{dissoc}} \times [L] \times [R] = \frac{[L]\times[R]}{K_D} \quad (6)$$

($K_D = \frac{K_{dissoc}}{K_{assoc}}$, equilibrium dissociation rate constant)

If $\frac{E}{E_{max}} \times R_T$ is substituted for LR, with the assumption of $E \propto LR$ ($\frac{E}{E_{max}} = \frac{[LR]}{[R_T]}$), differential equation for E can be derived using equation 5 as follows.

$$\frac{dE}{dt} = K_{assoc} \times [L] \times E_{max} - (K_{assoc} \times [L] + K_{dissoc}) \times E \quad (7)$$

The equation 7 can be applied to non-steady state experiments such as single dose pharmacokinetic and pharmacodynamic study in which the drug concentrations and responses were measured serially over time, as an example.

$$\text{Since } f_{LR} = \frac{[LR]}{[R_T]} = \frac{[LR]}{[R]+[LR]} = \frac{\frac{[L]\times[R]}{k_D}}{[R]+\left(\frac{[L]\times[R]}{k_D}\right)} = \frac{[L]}{k_D+[L]} = \frac{E}{E_{max}} \quad (8)$$

Where f_{LR} is fraction of receptor occupied by drug.

$E = \frac{Emax\times[L]}{K_D+[L]}$ can be obtained from equation 8. (9)

Operational model of agonism

The operational model of agonism introduces transducer function that is stimulated by ligand-receptor complex (not ligand itself), which elicits the drug effect following the same way with the above equation 9, which can be described by the following equation 10 at this time.

$$E = \frac{E_{max}\times[LR]}{K_E+[LR]} \quad (10)$$

Where E_{max} = maximal effect or response; E = effect elicited at a given level of occupancy, i.e., $[LR]$; K_E = value of $[LR]$ that elicits the half-maximal effect.

(Note that the L in equation 9 is replaced by LR in equation 10)

Substituting $\frac{R_T\times\boldsymbol{L}}{\boldsymbol{K_D}+\boldsymbol{L}}$ for LR in the equation 10 ($LR = \frac{R_T\times\boldsymbol{L}}{\boldsymbol{K_D}+\boldsymbol{L}}$) can be obtained from the equation 8), the following equation is derived.

$$E = \frac{E_{max}\times[R_T]\times[L]}{K_D K_E+([R_T]+[K_E])[L]} \quad (11)$$

Assuming that receptor occupancy can be described by a rectangular hyperbolic expression, Black and Leff showed that the transducer function, the functions that links occupancy to response, must be hyperbolic if the observed E/[L] relationship is hyperbolic.[3,4] An important component used in this model is the transducer ratio, τ (tau)

$$\tau = \frac{[R_T]}{K_E} \quad (12)$$

The transducer ratio measures the efficiency of the transduction of receptor occupancy to biological effects. τ is affected by the properties of the tissue, concentration of receptors, and the consequences of drug-receptor interaction, or in other words, the potency of an agonist to elicit a response is affected by both receptor affinity to the agonist and receptor efficiency in translating receptor occupancy to response.

$$E = \frac{E_{max}\times[R_T]\times[L]}{K_D\times K_E+(K_E+[R_T])\times[L]} = \frac{E_{max}\times\left(\frac{[R_T]}{K_E+[R_T]}\right)\times[L]}{\left(\frac{K_E}{K_E+[R_T]}\right)\times K_D+[L]} \quad (13)$$

If $R_T >> K_E$ (Spare receptor model), then

$$E = \frac{E_{max}\times[L]}{\left(\frac{K_E}{[R_T]}\right)\times K_D+[L]}$$

Since $\tau = \frac{[R_T]}{K_E}$,

$$E = \frac{E_{max}\times[L]\times\tau}{K_D+[L]\times\tau} \quad (14)$$

By substituting $\frac{E \times K_E}{E_{max} - E}$ (LR = $\frac{E \times K_E}{E_{max} - E}$ from equation 10) for *LR*, from equation 5, a differential equation below is obtained.

$$\frac{dE}{dt} = \frac{(E_{max} - E) \times \tau}{E_{max}} \times \left\{K_{assoc} \times L \times \left(\frac{(E_{max} - E) \times \tau - E}{\tau}\right) - \left(\frac{K_{dissoc} \times E}{\tau}\right)\right\} \quad (15)$$

The time-dependent differential equations derived in this tutorial would provide a framework for quantitative PK/PD modeling, which could be widely applied in pharmacological *in vitro* and non-clinical/clinical *in vivo* experiments for an agonist at non-steady state as well as steady state condition. This operational model of agonism could potentially provide critical information to predict optimal doses of agonists in various stages of clinical trials. For instance, it can potentially be used to obtain the most appropriate doses for future clinical trials including recommended starting dose for a first-in-human study, based on pharmacological *in vitro* and *in vivo* experiments at the early stage of drug development.

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Conflicts of interests

Authors: The authors declare that they have no conflict of interests
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