Mechanistic ligand-receptor interaction model: operational model of agonism

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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 phase of drug development.

Ligand-receptor interaction model
$L$ and $R$ are ligand and receptor, respectively:

$$[L] + [R] = [LR] \tag{1}$$

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

\[ E = \frac{E_{\text{max}} \times [L]}{K_E + [L]} \]  

(10)

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

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

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

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

(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, \( \tau \) (tau)

\[ \tau = \frac{[R_T]}{K_E} \]  

(12)

The transducer ratio measures the efficiency of the transduction of receptor occupancy to biological effects. \( \tau \) 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.

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

(13)

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

\[ E = \frac{E_{\text{max}} \times [L]}{K_D [R_T] + [L]} \]  

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

\[ E = \frac{E_{\text{max}} \times [L] \times \tau}{K_D [L] + \tau} \]  

(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.

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

(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
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