COMMENTARY

Systems Pharmacology Models for Guiding Drug Design

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Systems pharmacology models provide a quantitative framework for understanding the dynamic interplay among variables of complex biological systems affected by drugs and pathophysiological processes. New classes of drugs are developed that seek to exploit unique properties of single ligands targeting two (or multiple) receptors. The rational optimization of efficacy for such drugs requires expansion of the classical ligand–receptor binding models to account for physical properties of both ligand and receptors.

MODELING DOSE–EFFECT RELATIONSHIPS

Mathematical models of dose–effect relationships are based on the fundamental concept of receptor occupancy theory, stating that a pharmacological effect is mediated by receptors activated by drug binding, and its intensity is a function of the drug–receptor complex concentration. On drug binding, the activated receptor initiates a signaling cascade that leads to a desired pharmacological effect. Receptor occupancy is determined by specificity of the ligand for its receptor, strength of the binding, receptor inactivation, and the relative availability of the ligand and receptor. Common experimental techniques for the quantification of these processes include radioactive and fluorescent labeling, microscopy, and flow cytometry, as well as assays for drug and receptor concentrations. Such data provide grounds for quantitative analysis using mathematical models, and classical chemical reaction equations are capable of adequate description of receptor binding, internalization, and turnover. Under steady-state conditions, when the time scales for some processes (e.g., binding and dissociation) are relatively short, equilibrium assumptions are made allowing for the explicit calculation of concentrations of ligand, receptor, and ligand–receptor complexes. Such equations are presented in the majority of texts on enzyme kinetics and pharmacology. However, temporal sequence data can be affected by internalization of the drug–receptor complex due to endocytosis, followed by endosomal degradation and recycling. This dynamic receptor trafficking is an integral part of the receptor binding process and is also a subject of mathematical modeling. The measurements of proteins and enzymes in intracellular compartments provide sufficient information for characterizing the signaling events initiated by the activated receptor. The processes controlled by subsequent up/downregulation or activation/inactivation of proteins, such as cell cycle and apoptosis, determine the status of the cell. Mathematical models of signal transduction have been developed for variety of systems, such as signaling by the epidermal growth factor receptor (EGFR).

The outcomes of the signaling process can be linked, at least in theory, to the whole cell response such as cell proliferation or death. The distribution of individual cell responses can be quantified for the cell population and expressed as total number of cells exhibiting a characteristic of interest such as viability, activity, or any measurable feature. For example, cell number can represent a marker of drug efficacy in vitro. In this framework, empirical dose–effect relationships gain a mechanistic interpretation reflecting drug–receptor binding, trafficking, signal transduction, and cellular response as shown in Figure 1. This approach is a continuation of classical models explaining the relationship between drug concentration and pharmacological effect initiated by Clark’s occupancy theory, followed by Arien’s concept of intrinsic activity, and Black and Left’s theory of operational agonism that has been applied in temporal pharmacokinetic and pharmacodynamic models.

MODELING DRUG BINDING TO CELL SURFACE RECEPTORS

Quantitative pharmacology provides a means for understanding and optimizing receptor occupancy, and the actual drug-binding process is often the primary focus of such models. Specific binding of a ligand to a receptor is typically represented by a bimolecular reaction, the rate of which is proportional to ligand and receptor concentrations and is characterized by a second-order association rate constant $k_{on}$. The dissociation of the drug–receptor complex is assumed to be a first-order process ($k_{off}$). However, ligand–receptor binding is not a simple chemical process in isolation. Physical features of the system such as molecular transport, presence of multiple binding sites, and stochastic effects can significantly influence rates of ligand binding. As shown for chimeric drugs, localization of receptors and ligands can influence the apparent binding properties of drugs. The binding of two molecules is a two-step process that starts with the molecular transport of ligand and receptor into proximity before the chemical binding reaction step. The transport rate constant $k_T$ is primarily determined by diffusion, whereas the chemical reaction rates are defined by $k_{on}$ and $k_{off}$ constants. The ligand association constant thereby becomes a function of $k_T$ and $k_{on}$ as a solution to combined diffusion and chemical reaction equations. The diffusion process is governed by a diffusion coefficient and the geometric characteristics of the...
MODEL-BASED DESIGN OF CHIMERIC DRUGS

A new type of chimeric protein has been engineered to ensure both specificity and affinity to two membrane-bound receptors. It consists of targeting and activity elements connected by a protein linker. The rationale for combining two ligands was to counter weak binding of an activity element binding to two distinct membrane receptors, becoming a ternary system with ligand binding to cell surface receptors and diffusion properties impacting drug–receptor binding. Mathematical models are essential for integrating system components for the rational design of such drug molecules, optimizing their selectivity for target receptors.

Figure 1 Schematic diagram representing steps in systems pharmacology modeling of drug–effect relationships. Drug–receptor binding: Ligand (L) and receptor (R) molecules are transported into proximity where intrinsic reactions of association ($k_{on}$) and dissociation ($k_{off}$) occur. Receptor trafficking and turnover: Ligand–receptor complex (C) is internalized by endocytosis. In the endosome, the complex can become dissociated and sorted, and ligand and receptor molecules are recycled ($k_{rec}$) or degraded ($k_{deg}$). New receptors are synthesized in the cell cytosol ($k_{syn}$). Signal transduction: The ligand–receptor complex initiates a signaling cascade by activation of G-proteins or enzymes (E, inactive; $E^*$, active), which can activate other enzymes and secondary messengers (e.g., protein kinases) leading to an up or downregulation of genes, transcribed further to mRNA. Subsequently, mRNA is translated to functional proteins (P) that can affect the cell status. Cellular response: the effector proteins can alter cell turnover (e.g., induce cell death or proliferation) and/ or function. These processes change the optical intensity of a marker distributed among all cells and their total count is a measure of the pharmacological effect.

receptor such as the encounter radius. Complexity of the system increases because transport properties are different for receptors and ligands in free solution vs. bound to a cell surface. The latter case is critical when drug is able to bind to two distinct membrane receptors, becoming a ternary system that additionally requires an average distance between receptors to be considered. Consequently, receptor and ligand geometry, density of their expression on the cell membrane, and diffusion properties impact drug–receptor binding. Mathematical models are essential for integrating system components for the rational design of such drug molecules, optimizing their selectivity for target receptors.

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