Time-dependent ligand-receptor binding kinetics and functionality in a heterodimeric receptor model

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Abstract

G protein-coupled receptors (GPCRs) are membrane proteins that transmit the chemical signal embodied in the molecular structure of neurotransmitters, hormones and synthetic ligands from outside to inside the cell. GPCRs are therefore involved in many cellular processes that are crucial in physiological and pathological conditions. There is growing evidence that GPCRs heteromerize both in CNS and non-CNS regions. This structural complexity provides a mechanistic framework in which drug combination therapies can be explored. In this communication, a heterodimer model of differential equations representing the time-dependent binding of two ligands (A and B) to a receptor heterodimer (R_1R_2) is considered. This pharmacological model can quantify the cooperativity interactions between ligands A and B through the heterodimer interface thus providing a mathematical tool in which the synergistic effects observed in some drug combination therapies can be mechanistically explained. We analyze the system under two pharmacological conditions: (i) both ligands are in excess and (ii) only one ligand is in excess with respect to receptor concentration, where the latter condition is proposed for those situations in which one of the ligands elicits unwanted side effects and lowering its concentration is a necessary requirement. We prove the existence of a unique biologically plausible equilibrium in a wide region of the parameter space formed by the association and dissociation rate constants of the model, thus ensuring a feasible pharmacological scenario when exploring the optimal set of rate constants for a specific drug combination therapy. Moreover, the time dynamics of the biological response shows different behaviors depending on the intrinsic efficacies of the four heterodimeric species (R_1R_2, AR_1R_2, R_1R_2B, AR_1R_2B), and this can be used to explore the potential utility of drug combinations.

References

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