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Kinetic regulation of multi-ligand binding proteins

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Abstract

© 2016 Salakhieva et al.Background: Second messengers, such as calcium, regulate the activity of multisite binding proteins in a concentration-dependent manner. For example, calcium binding has been shown to induce conformational transitions in the calcium-dependent protein calmodulin, under steady state conditions. However, intracellular concentrations of these second messengers are often subject to rapid change. The mechanisms underlying dynamic ligand-dependent regulation of multisite proteins require further elucidation. Results: In this study, a computational analysis of multisite protein kinetics in response to rapid changes in ligand concentrations is presented. Two major physiological scenarios are investigated: i) Ligand concentration is abundant and the ligand-multisite protein binding does not affect free ligand concentration, ii) Ligand concentration is of the same order of magnitude as the interacting multisite protein concentration and does not change. Therefore, buffering effects significantly influence the amounts of free ligands. For each of these scenarios the influence of the number of binding sites, the temporal effects on intermediate apo- and fully saturated conformations and the multisite regulatory effects on target proteins are investigated. Conclusions: The developed models allow for a novel and accurate interpretation of concentration and pressure jump-dependent kinetic experiments. The presented model makes predictions for the temporal distribution of multisite protein conformations in complex with variable numbers of ligands. Furthermore, it derives the characteristic time and the dynamics for the kinetic responses elicited by a ligand concentration change as a function of ligand concentration and the number of ligand binding sites. Effector proteins regulated by multisite ligand binding are shown to depend on ligand concentration in a highly nonlinear fashion.

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Keywords

Calcium, Calmodulin, Ligand-receptor binding, Transient kinetics