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A simple reaction kinetic model of rapid (G protein dependent) and slow (β-Arrestin dependent) transmission

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ABSTRACT

In this paper the qualitative dynamic behavior of reaction kinetic models of G protein signaling is examined. A simplified basic G protein signaling structure is defined, which is extended to be able to take the effect of slow transmission, RGS mediated feedback regulation and ERK-phosphatase mediated feedback regulation into account.

The resulting model gives rise to an acceptable qualitative approximation of the G protein dependent and independent ERK activation dynamics that is in good agreement with the experimentally observed behavior.

1. Introduction

Diverse signaling molecules, including neurotransmitters, hormones, phospholipids, photons, odorants, taste ligands and mitogens, bind to their specific G protein-coupled receptors (GPCRs), also known as seven-transmembrane receptors (7TMRs), in the membrane of the target cells, which subsequently interact with their respective G proteins to induce a cascade of downstream, i.e. intracellular signaling.

The G proteins are heterotrimeric signaling molecules composed of three subunits, α, β and γ, which dissociate upon receptor-induced exchange of GDP for GTP on the α subunit ($G\alpha$) to form a free $G\alpha$ and a dimer of $G\beta\gamma$ subunits (Gutkind, 1998a, b; Luttrell et al., 1999). Many isoforms of these subunits have been cloned in the past years and have been classified into four groups according to the subtype of their α subunit: $G\alpha s$, $G\alpha i$, $G\alpha q$ and $G\alpha 12$. All these $G\alpha$ subunits, as well as the dissociated $\beta\gamma$ subunits, and other receptor-interacting proteins are capable of initiating diverse downstream signaling pathways via second messenger molecules, such as cyclic AMP, inositol triphosphate, diacylglycerol, and calcium.

Activation of the signal induced by the GPCR depends on the rate at which ligand-bound receptor catalyzes exchange of GDP for GTP on the $G\alpha$ subunit. Following exchange, GTP-bound $G\alpha$ dissociates, at least partially, from both the receptor and $G\beta\gamma$ complex. The length of time that $G\alpha$GTP and $G\beta\gamma$ can interact with effectors is determined by the rate at which $G\alpha$ hydrolyzes GTP to GDP. Following hydrolysis, inactive $G\alpha$GDP binds $G\beta\gamma$ with high affinity, and terminates $G\beta\gamma$ signaling. GTPase-activating proteins (GAPs) speed up the hydrolysis of GTP by $G\alpha$ (Zerangue and Jan, 1998). In this article $G\beta\gamma$ signaling events are not examined.

The most accepted classic paradigm of signaling until nowadays has been that the significantly important elements which contribute to information transfer into the internal system of the cell are the α and $\beta\gamma$ subunits of G proteins (see the review Lefkowitz, 2004). This paradigm was in good agreement with the classical concept of drug efficacy in the context of receptor-occupancy theory where the efficacy is considered as an intrinsic property of the ligand–receptor pair (Galandrin et al., 2007).

One of the most important main targets of the intracellular pathways affected by G protein related signaling is the family of MAPK/ERK cascades (Huang and Ferrell, 1996; Kolch et al., 2005; Zou et al., 2008). Proteins called G protein-coupled receptor kinases (GRKs) are able to rapidly terminate this signaling response via phosphorylating the receptor, typically on its cytoplasmic tail (Pitcher et al., 1998). Following phosphorylation, β-Arrestins bind the receptor, which blocks further G protein-initiated signaling.

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In recent years it has been shown that β-Arrestins not only take part in receptor desensitization (Freedman and Lefkowitz, 1996), but form an endocytic protein complex, which initiates a G protein independent regulation of ERK (DeFea et al., 2000; Luttrell et al., 2001; Beaulieu et al., 2005). The recognition that a single receptor acts as multiple source of signaling pathways and various drugs binding to this receptor might differentially influence each of this pathways (in contrast to pathway-specific drugs), led to the reassessment of the efficacy concept (Galandrin et al., 2007).

Another important mechanism contributing to the dynamics of signaling is the feedback regulation, about which there are only a few models available in the literature (Krauker et al., 2002; Zhong et al., 2003). At the same time, efforts to take into account the β-Arrestin dependent slow transmission as a second pathway convergent to G protein signaling is not prevalent either in literature.

Much effort has been made nowadays to find plausible mathematical models for the description of G protein related signaling dynamics (Adams et al., 1998; Riccobene et al., 1999; Woolf and Linderman, 2000; Woolf et al., 2001, 2000; Linderman, 2000; Chen et al., 2003; Kinzer-Ursem and Linderman, 2007), in order to analyze signaling dynamics and ligand efficacy, and lay down the fundamentals of dynamical pharmacology (Aradi and Érdi, 2006).

To join the above-mentioned efforts, the aim of our paper is to propose a simple (in a sense minimal) reaction kinetic model and the implied equations for G protein signaling, based on biochemical and physiological observations collected about cell signaling pathways corresponding to a simplified model of fast-, and slow-transmission as well as the regulation of G protein signaling that is able to reproduce the downstream activation pattern (like ERK or Akt) recently described in DeWire et al. (2007) qualitatively. Our modeling effort is directed towards describing the dynamics, i.e. the time evolution of the key components participating in G protein dependent and independent signaling. This enables to apply control theoretic methods for finding optimal drug dosing strategies in the future.

We aim at constructing a model in strict reaction kinetic form, in order to stay in a model class for which the deficiency-based multistability-related results of Feinberg (2004) and Craciun and Feinberg (2006a, b) can be applied in the future. These results provide very strong theorems about qualitative behavior of reaction kinetic systems, based only on the structure of the reaction network, independent of its parameters. Furthermore, these and other (Tyson et al., 2001, 2003) multistability-related results offer the possibility to explain interesting physiological phenomena related to typical dynamic, pulsatile intercellular signals, for example, in the case of GnRH-affected gonadotropine cells (Williams et al., 1990), or dopamine-affected prolactin cells (Ben-Jonathan and Hnasko, 2001).

2. Basic model structure of the G protein signaling mechanism

The most simple reaction kinetic model of G protein signaling is constructed in this section, which is able to describe ligand binding, $G\alpha$ activation, deactivation and reactivation. Furthermore, the model contains the $G\alpha$ uncoupled ligand-bound receptor that enables to extend the model with slow transmission related reactions in the following sections.

In order to simplify the form of the equations, the notations in Table 1 for species is introduced, with the notation C_i used for complexes.

For the development of a simple mathematical model of basic G protein signaling, the reaction scheme depicted in Fig. 1 is used.

Table 1
Notations in the basic model

Specie	Notation
R(Gα-GDP)	*A*
L	*B*
R(Gα-GTP)L	C_1
RL	*D*
(Gα-GTP)	*E*
(Gα-GDP)	*F*
R	*G*

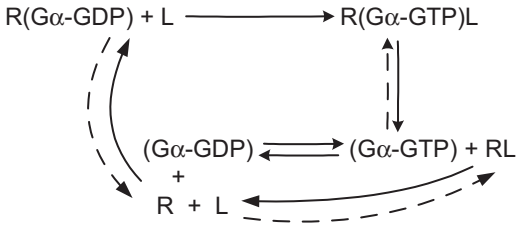

Fig. 1. The reaction scheme of G protein signaling.

It can be clearly seen from the reaction scheme in Fig. 1 that the model does not describe active and inactive receptor forms, as for example the models detailed in Chen et al. (2003) and Riccobene et al. (1999). The reason for this lays in the fact that in this study the properties of the ligand corresponding to achieve conformational changes in the receptor are not of primary interest, but the qualitative features of the two (G protein dependent and independent slow transmission) signaling pathways, and the feedback regulation of signaling will be in the focus. According to this aim, it can be assumed that conformation change of the receptor always appears after ligand binding, and is always followed by GDP/GTP exchange on the α subunit.

It is important to note that the primary input of the model is the ligand concentration on the cell surface, however, in the later sections GRK concentration will also be considered as input. The *Gα-GTP*, and later the ERK activation corresponds to the output of the system.

2.1. Modeling assumptions

The basic model describes a cell together with the cell surface, and the only component for which the system is open, is the ligand. This can be understood as the effect of the cell's environment that influences the ligand concentration on the cell surface (if the ligand concentration in the environment rises, the ligand concentration on the cell surface will rise too).

For all other components, the system is closed. This can be described by the following conservation equations (see notations in Table 1):

- The conservation of G protein: $[G\alpha^{tot}] = [A] + [C_1] + [E] + [F]$.
- The conservation of receptors: $[R^{tot}] = [A] + [C_1] + [D] + [G]$.
- The conservation of the ligand: $[L^{tot}] = [B] + [C_1] + [D]$.

The dynamic time-dependent or state variables of the system are the concentrations of the complexes, and the reactions in the system obey the mass action law.