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An ODE Model of Dopamine Receptor Availability and Trafficking

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Abstract. The dopaminergic system has been extensively studied for 40 years as it affects vital neurological, gastrointestinal, cardiovascular and renal processes, among others. It has been observed that disorders in the dopamine receptor system can be associated to the failure of dopamine to inhibit various processes that leads to serious pathological conditions such as Parkinson's disease, schizophrenia and hypertension, among others. This paper presents an ordinary differential equation (ODE) model of dopamine receptor availability and intracellular trafficking derived from Zeng et al (2004) including receptor activation, desensitization, internalization, degradation and recycling. The proposed model will illustrate the dynamics of receptor trafficking and the effects of various mechanisms that affect cell surface receptor availability.

Keywords: Receptor availability, Receptor trafficking, Dopamine receptors

1. Introduction

Dopamine, an important catecholamine, has been identified to control primary physiological and metabolic processes in the human body, such as locomotion, hormone secretion, behavior, as well as various gastrointestinal, renal and cardiovascular functions. Because of its significance, this chemical substance and its effects to various bodily processes has been studied for the past 40 years. Based on these researches, it has been observed that there is a positive correlation between the disorders regarding dopamine receptor function and the failure of dopamine to block hallucinations in schizophrenic subjects, or to increase sodium excretion in hypertensive subjects, among other bodily functions.

The focus of the dopamine research of the last 20 years has been to discover drugs with less or no side effects. The efforts have significantly contributed to our understanding of the dopaminergic system, but studies regarding the dynamics of dopamine receptor system in a particular time period are very limited in the literature.

This paper presents an ordinary differential equation (ODE) model of dopamine receptor availability and trafficking derived from [11]. The model presents the mechanisms of receptor trafficking, including G protein-coupled receptor activation, desensitization, internalization and recycling.

With the proposed model, the availability of the free and internalized receptors on the cell surface can be determined at any given time. Moreover, the effects of receptor activation, desensitization, internalization and recycling to its availability can also be explored in the model.

2. Modeling Framework

2.1. Biochemical Systems Theory (BST)

The Biochemical Systems Theory (BST) is a methodology in which the reaction rates (fluxes) are represented using power law expansions in the system variables [9]. This structure permits mathematical

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analyses of biochemical networks under a minimal set of assumptions and the resulting model are based solely on the identity of the reactants (molecular species) and their regulatory interconnections.

In this paper, the ODEs are derived following the rules of traditional mass-action kinetics under BST, that is, the rate of change of a certain concentration is given by the difference of the influxes and the effluxes of the system.

2.2. Mechanisms of Dopamine Receptor Availability and Trafficking

Various studies describe the dynamics of the dopamine receptor system, such as [2], 3, 6, 11]. In 2004, Zeng et al [11] presented a schematic representation of the renal dopamine receptor system, shown in Figure 1. Although this diagram has been mainly used in constructing the mathematical model, the behavior of dopamine receptor system is similar in other parts of the human body, and thus can also be generally used.

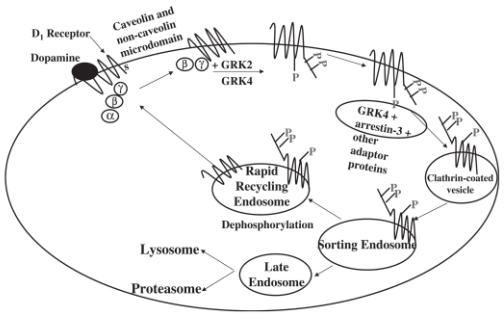

Fig. 1: Biological Model of Dopamine Receptor Trafficking [11]

As detailed in [5], [11], the process starts with the dopamine binding to its receptor, forming a ligand-receptor complex, followed by receptor desensitization by G protein-coupled receptor kinases (GRKs), association of β-arrestin and other adaptor proteins before internalization (endocytosis) in the early endosome. Then, the interaction of the dopamine receptor with proteins in the early endosome sends them either to the late endosome for lysosomal or proteasomal degradation, or to the rapid recycling endosome for dephosphorylation before it is recycled back to the cell surface. It has been observed that dephosphorylation can also occur in the plasma membrane.

2.3. Construction of the Model

2.3.1. Receptor Trafficking Model with Endocytosis Cycle

In 1993, Lauffenburger and Linderman [4] proposed a model of receptor trafficking with simple receptor activation, internalization, recycling and degradation, and is illustrated in Figure 2. The process begins with ligand and receptor production with rates V_L and V_R, respectively. Ligands bind with the free receptors with forward and backward rates of k_{on} and k_{off}, respectively, followed by internalization of complexes to the endosome at the rate of k_{eC}. Free receptors are also internalized at the rate of k_{eR}. From the endosome, the receptors and/or ligands are either sent to the lysosome for degradation at the rate of k_{deg}, or recycled back to the cell surface at the rate of k_{rec}. The ligand uptake is excluded in the model from [4] since the process is not specified in [11].

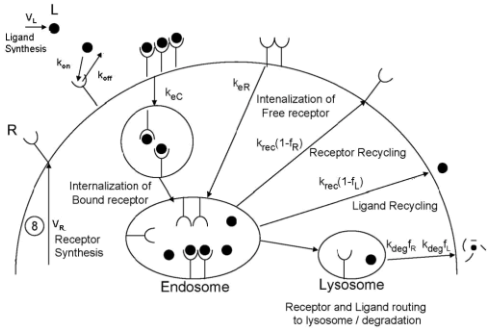

Fig. 2: Receptor Trafficking Model with Endocytosis Cycle [4]

2.3.2. GPCR Trafficking Model with Desensitization and Phosphorylation

The generally accepted paradigm for the trafficking of GPCRs, which includes the dopamine receptors, begins with ligand-receptor binding, followed by receptor desensitization through a change in receptor conformation, modification and/or phosphorylation [10]. Note that desensitization is proposed to be a feedback mechanism to protect against both acute and chronic overstimulation [8].

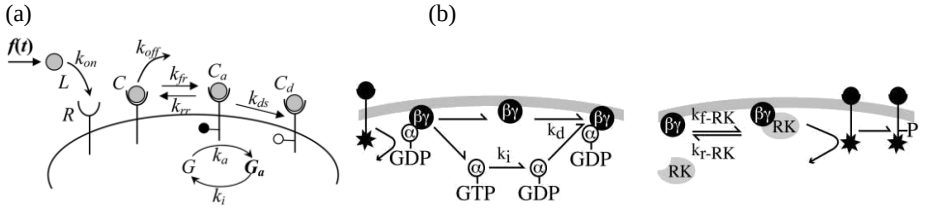

Fig. 3: (a) GPCR Activation and Desensitization Model [8]; (b) Role of GRK in GPCR Phosphorylation

Figure 3a illustrates a GPCR activation and desensitization model from [8], and is similar to Figure 2. The model starts with the ligand-receptor binding to yield inactive complexes C, followed by its activation, producing active complexes C_a with forward rate k_{fr} and reverse-rate k_{rr}. Then, C_a are irreversibly desensitized at rate k_{ds}. Moreover, C_a are also capable of converting inactive G-protein molecules G to the active form G_a with a second-order forward rate constant k_a and reverse rate k_i.

Moreover, Woolf and Linderman [10] considered the role of GRK in the GPCR phosphorylation. In Figure 3b, RK binds to the active Gβγ subunit of G protein to initiate phosphorylation, with rate $k_{f\text{-}RK}$, and unbinds with rate $k_{r\text{-}RK}$.

3. The Model

3.1. Assumptions

The rapid recycling endosome, which is responsible for the dephosphorylation of the receptors before these are recycled to the cell surface, are excluded in the proposed kinetic model. The dephosphorylation process is then assumed to occur in the plasma membrane, and its reaction rate is factored in the recycling rate k_{rec}. This further implies that the recycled ligands and receptors from the early endosome will be available in the cell surface at the same time.

3.2. Kinetic Model Representation

The kinetic model of dopamine receptor trafficking, derived from [11], is constructed by combining the activation, internalization, degradation and recycling steps from Figure 2, with the GPCR activation, desensitization and phosphorylation steps from Fig. 3(a) and 3(b). The diagram is shown in Fig. 4 below.

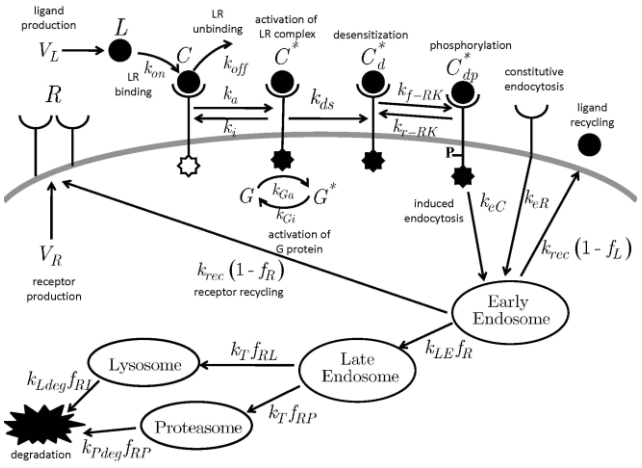

Fig. 4: Kinetic Model of Dopamine Receptor Trafficking

Legend:

R_S - number of receptors at the surface
C - number of inactive complexes at the surface
C^* - number of active complexes at the surface
C^*_d - number of desensitized complexes
C^*_{dp}- number of phosphorylated complexes
R_{Ti} - number of internalized receptors (to the EE)
L_{Ti} - number of internalized ligands (to the EE[2])
k_{on} - forward rate to yield inactive complexes C
k_{off} - reverse rate to yield inactive complexes C
k_a - activation rate to yield active complexes C^*
k_i - inactivation rate to yield active complexes C^*
k_{Ga} - conversion rate from G to G^*
k_{Gi} - conversion rate from G^* to G
k_{ds} - rate of desensitization
$k_{f\text{-}RK}$ - rate of binding of Gβγ subunits and GRK
$k_{r\text{-}RK}$ - rate of unbinding of Gβγ subunits and GRK
k_{eC} - internalization rate of the complexes
k_{eR} - internalization rate of the free receptors
k_{rec} - rate of ligand and receptor recycling to the PM[1]
k_{LE} - rate of transfer from the EE[2] to the LE[3]
f_R - fraction of R_{Ti} that will be sent to the LE[3]
f_L - fraction of L_{Ti} that will be sent to the LE[3]
k_{TL} - rate of transfer from the LE[3] to the lysosome
k_{TP} - rate of transfer from the LE[3] to the proteasome
f_{RL} -fraction of R_{Ti} that is sent to the lysosome
f_{RP} -fraction of R_{Ti} that is sent to the proteasome
k_{Ldeg} - rate of lysosomal degradation
k_{Pdeg} - rate of proteasomal degradation
V_R - rate of receptor synthesis
V_L - rate of ligand synthesis
N_{av}- Avogadro's number (6.022×10^{23} molecules/M)

[1]PM: plasma membrane; [2]EE: early/sorting endosome;
[3]LE: late endosome

3.3. Flux Balance Equations

This section presents the balance equations of the different primary components of the dopamine receptor system, namely the rate of change of the concentration of free (1) and internalized receptors (2), the free (3) and internalized ligands (4), the inactive (5), active (6), and phosphorylated (7) complexes, the and the number of active G proteins (8) at a particular time. Moreover, the rate of change of number of recycled receptors (9) and receptors sent to the lysosome (10), and proteasome (11) for degradation, are also presented below.

$$\frac{dR_S}{dt} = -k_{on}R_S L + k_{off}C - k_{eR}R_S + k_{rec}(1-f_R)R_S + V_R \quad (1)$$

$$\frac{dR_{Ti}}{dt} = k_{eC}C^*_{dp} + k_{eR}R_S - k_{rec}(1-f_R)R_S - k_{LE}f_R R_{Ti} \quad (2)$$

$$\frac{dL_S}{dt} = (N_{av}V)(-k_{on}R_S L + k_{off}C) + V_L \quad (3)$$

$$\frac{dL_{Ti}}{dt} = k_{eC}C^*_{dp} - k_{rec}(1-f_R)R_S - k_{LE}f_R R_{Ti} \quad (4)$$

$$\frac{dC}{dt} = k_{on}R_S L - k_{off}C - k_a C + k_i C^* \quad (5)$$

$$\frac{dC^*}{dt} = k_a C - k_i C^* - k_{ds}C^* \quad (6)$$

$$\frac{dC^*_{dp}}{dt} = k_{f-RK}C^*_d - k_{r-RK}C^*_{dp} - k_{eC}C^*_{dp} \quad (7)$$

$$\frac{dG^*}{dt} = k_{Ga}GC^* - k_{Gi}G \quad (8)$$

$$\frac{dR_{rec}}{dt} = k_{rec}\left[(1-f_R)\left(k_{eC}C^*_{dp} + k_{eR}R_S\right)\right] \quad (9)$$

$$\frac{dR_{lys}}{dt} = k_{LE}f_{RL}\left(k_T - k_{deg}\right)\left(C^*_{dp} + R_S\right) \quad (10)$$

$$\frac{dR_{prot}}{dt} = k_{LE}f_{RP}\left(k_T - k_{deg}\right)\left(C^*_{dp} + R_S\right) \quad (11)$$

In the construction of the ODE system, it is further assumed that the ligand concentration is measured in terms of its molar concentration, thus multiplying the associated equations by the Avogadro's number and the volume of the cell, as most experiments measure its abundance in molar units. The other species are counted by their number (molecular count) per unit time.

Moreover, the change of the internalized ligands is expressed in terms of the receptor count as they are sent to the early endosome and/or recycled to the plasma membrane after binding with its receptor. The other equations are modelled similarly.

4. Conclusion

In this paper, an ODE model of cell surface dopamine receptor availability and intracellular trafficking is presented to comprehensively illustrate the dynamics of the dopamine receptor system. This model will help the experimenters distinguish particular molecular species and/or subprocesses that significantly affect the

regulation and transmission of the receptor system. However, the model needs further refinement and validation through various experiments so that it will be useful to illustrate the dynamics of the dopamine receptor system *in silico.*

5. Recommendations

As the constructed ODE model is yet theoretical, it needs specific experimental values, such as reaction rates and initial concentrations, to compute for the specific rates of change of the different molecular species, so that the behaviour of the system can be determined at different time points, and to further verify that the results agree with the corresponding *in vivo* experimental observations.

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