MATHEMATICAL MODELING
OF RECEPTOR MEDIATED ENDOCYTOSIS
OF LOW-DENSITY LIPOPROTEINS
AND THEIR DEGRADATION IN LYSOSOMES

Ratushny A.V. *
Institute of Cytology and Genetics, SB RAS, Novosibirsk, 630090, Russia
* Corresponding author: e-mail: ratushny@bionet.nsc.ru

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SUMMARY

Motivation: Receptor-mediated endocytosis of low-density lipoproteins (LDL), their transport within endosomes, and subsequent degradation in lysosomes are essential components of the molecular system for cholesterol homeostasis in vertebrate cells. Construction of a detailed mathematical model of these processes would allow comprehensive study of their molecular mechanisms and evaluation of the effect of various mutations and disorders of this system on the gene net controlling intracellular cholesterol homeostasis.

Results: The receptor-mediated endocytosis of LDL particles and their subsequent degradation in the cell has been modeled. The network of mono- and bimolecular reactions best describing the system has been constructed. The results of calculation of kinetic parameters of the molecular system derived from the model are in agreement with experimental evidence.

INTRODUCTION

Receptor-mediated endocytosis of LDL particles and their subsequent degradation in lysosomes involve at least seven stages: (1) exposure of synthesized receptor molecules on the cell surface; (2) binding of the receptor to the ligand (LDL particle); (3) internalization of the LDL-receptor complex; (4) dissociation of the receptor from the ligand; (5) return of the receptor on the cell surface; (6) fusion between endosomes and lysosomes; (7) degradation of LDL in lysosomes to amino acids, cholesterol, and other lipids (Brown, Goldstein, 1979).

We developed a mathematical model of receptor-mediated endocytosis of LDL particles and their subsequent degradation in the cell. A sequence of mono- and bimolecular reactions was developed to provide an adequate description of the system under study in terms of chemical kinetics. The results of calculation of kinetic parameters of the components of the molecular system derived from the model are in agreement with experimental evidence.
METHODS AND ALGORITHMS

The generalized chemical-kinetic method (Likhoshvai et al., 2001) was used for simulation of receptor-mediated endocytosis of LDL particles, their transport within endosomes, and subsequent degradation in lysosomes.

RESULTS

A minimal mathematical model of receptor-mediated endocytosis of LDL particles and their subsequent degradation in the cell was constructed in terms of mono- and bimolecular reactions as shown in Fig. 1a. In the model, all receptors on the cell surface are internalized at a certain rate, including those not associated with the ligand. All internalized LDL within endosomes reach lysosomes at a certain speed to be degraded there.

![Diagram](image1.png)

**Figure 1.** (a) Scheme I. Receptor-mediated endocytosis of LDL particles followed by LDL degradation in lysosomes (for details see text). (b) Comparison of the results of simulation according to scheme I (panel a) with experimental data on the kinetics of receptor internalization and LDL degradation in the cell (Brown, Goldstein, 1979). Experimental data are designated as follows: • – amount of receptor-bound LDL particles on the cell surface; ▲ – internalized LDL concentration; ■ – degraded LDL concentration. Simulation results are shown with solid curves.

Fig. 1b presents the results of simulation according to the model under discussion compared with experimental data on the kinetics of receptor internalization and LDL degradation in the cell. The Fig. shows that the simulation does not illustrate the experimental data (Brown, Goldstein, 1979) quite perfectly. The simulation assumes exponential decrease in the concentration of ligand-bound receptors on the cell surface, so that the kinetic curve of LDL degradation does not flatten out within the time span of measurements from 5 to 30 min.

Analysis of the kinetic curves obtained by Brown and Goldstein (1979) and shown in Fig. 1b suggests that not all receptors on the cell surface can be internalized during endocytosis. The experiment shows that endocytosis is confined to certain sites on the plasma membrane. These sites are known as coated pits (Roth, Porter, 1964), and their
formation involves the protein clathrin (Pearse, 1975). Coated pits cover about 2% of the surface of human fibroblasts and contain 50 to 80% of LDL receptors (Orci et al., 1978). This fact provides an explanation for the kinetic curves (Figs. 1b and 2b) for internalization of LDL-bound receptors. Rapid uptake of 70–80% of the receptors occurs within the first 5–10 min. In the simulation, the mean time of the first stage of endocytosis (invagination of the coated pit together with receptors and its uptake into the cells) is estimated to be 2 min. The subsequent flattening-out of the kinetic curve is determined by buffering of the system owing to receptors not reaching coated pits during diffusion. To correct for this fact in the model, receptors on the cell surface are divided into two exchanging pools. Receptors of the first pool are located outside coated pits; thus, they are not involved in endocytosis, and vice versa (Fig. 2a).

It is known that after internalization bordered vesicles interact with small cellular organelles, smooth vesicles, to form endosomes (Klimov, Nikul’cheva, 1999). We explain the flattened kinetics of the concentration of uptaken LDL within the time span of measurement, 5–30 min, by the fact that LDL particles within endosomes cannot immediately reach lysosomes, which contain LDL-degrading enzymes. Actually, a lag occurs that is related to the time required for LDL transport by endosomes to lysosomes. To take into account the LDL delivery lag, the model includes four endosome pools passing into one another, and a “deadlock” pool, which mimics a certain amount of undegraded LDL in the cell. As shown in Fig. 2b, LDL degradation slows down after the second hour of measurements and virtually flattens out. The mean time of pass from one endosome pool to the next one in the simulation is taken to be ca. 8 min. The release of LDL receptors from ligands in the simulation occurs at the first stage owing to the acidic pH (~5) in endosomes (Klimov, Nikul’cheva, 1999). The time of receptor return on the cell surface is taken to be ca. 10 min. The overall time of receptor recycling is 20 min (2+8+10), which is in agreement with experimental evidence (Klimov, Nikul’cheva, 1999). The mean time of LDL degradation in the lysosome and release of about
475 cholesterol molecules and 1310 cholesterol ester molecules was estimated from the kinetic curve of LDL degradation in the cell (Fig. 2b, ■) and taken to be ca. 1 min.

Thus the new model constructed according to the processes schematically presented in Fig. 2a takes the form:

\[
\begin{align*}
\frac{dx_1}{dt} &= -k_1 \cdot x_1 \cdot x_2 + k_2 \cdot x_3 \cdot x_4 + k_4 \cdot x_6 \cdot x_7 \\
\frac{dx_2}{dt} &= -k_1 \cdot x_1 \cdot x_2 + k_3 \cdot x_4 + k_5 \cdot x_8 \\
\frac{dx_3}{dt} &= k_1 \cdot x_1 \cdot x_2 - k_1 \cdot x_4 + k_5 \cdot x_8 \\
\frac{dx_4}{dt} &= -k_1 \cdot x_1 \cdot x_4 - k_1 \cdot x_2 - (k_6 + k_7) \cdot x_9 \\
\frac{dx_5}{dt} &= -k_1 \cdot x_1 \cdot x_4 + k_5 \cdot x_8 - (k_6 + k_7) \cdot x_9 \\
\frac{dx_6}{dt} &= k_1 \cdot x_4 - k_1 \cdot x_9 \\
\frac{dx_7}{dt} &= k_1 \cdot x_9 - k_1 \cdot x_8
\end{align*}
\]

\[
\begin{align*}
\frac{dx_9}{dt} &= k_1 \cdot (x_6 + x_7) - k_9 \cdot x_9 \\
\frac{dx_{10}}{dt} &= k_1 \cdot (x_6 + x_11) \\
\frac{dx_{11}}{dt} &= k_1 \cdot (x_6 + x_{12}) - k_9 \cdot x_{12} + k_{10} \cdot x_{13} \\
\frac{dx_{12}}{dt} &= k_1 \cdot (x_6 + x_{13}) - k_9 \cdot x_{13} + k_{10} \cdot x_{14} \\
\frac{dx_{13}}{dt} &= k_1 \cdot (x_6 + x_{14}) - k_9 \cdot x_{14} + k_{10} \cdot x_{15} \\
\frac{dx_{14}}{dt} &= k_1 \cdot (x_6 + x_{15}) - k_9 \cdot x_{15} + k_{10} \cdot x_{16}
\end{align*}
\]

where \(x_i\) are concentrations of LDL particles and their receptors in corresponding states (Fig. 2a) and \(k_i\) are constants of the processes presented in Fig. 2a.

Model (1) describes the experimental evidence on the kinetics of LDL internalization and degradation more precisely (Fig. 2b). The kinetic curves were simulated for the following parameters: \(k_1 = 1.11 \cdot 10^{-5}\) (molecules/cell) \(\cdot s^{-1}\), \(k_2 = 10^{-4}\) s\(^{-1}\), \(k_3 = 3 \cdot 10^{-4}\) s\(^{-1}\), \(k_4 = 10^{-2}\) s\(^{-1}\), \(k_5 = 2 \cdot 10^{-3}\) s\(^{-1}\), \(k_6 = 2 \cdot 10^{-3}\) s\(^{-1}\), \(k_7 = 1.67 \cdot 10^{-3}\) s\(^{-1}\), \(k_8 = 5 \cdot 10^{-4}\) s\(^{-1}\), \(k_9 = 10^{-5}\) s\(^{-1}\), and \(k_{10} = 2.78 \cdot 10^{-2}\) s\(^{-1}\). Nevertheless, the uptake of receptors on the cell surface in this simulation from the first to second hour of measurement slightly exceeds the experimental values (Fig. 2b, ●). To correct this discrepancy, we accept an addition pool of receptors on the cell surface. This corrected model allows virtually perfect agreement with experimental data (data not shown).

Although this model provides a more precise description of the actual situation, it raises several questions lacking unambiguous answers, for example: how to describe receptor exposure on the cell surface, to what pool they come, and how they are distributed. To meet these questions, we accept the previous model, which provides simple answers. As the area of coated pits constitutes about 2% of the cell surface, it is safe to assume that receptor exposure occurs mainly outside them.

**DISCUSSION**

A mathematical model of receptor-mediated endocytosis of LDL proteins, endosome transport, LDL degradation in lysosomes, and regeneration of LDL receptors on the cell surface has been constructed and tested. The example of this model illustrates the importance of consideration of buffering and delay, occurring in each living organism and reflecting the actual kinetics (response time etc.) of cell operation. Neglect of these features of living systems highly probably results in errors in the description of the behavior of a system under study.

Receptor-mediated endocytosis is essential for many cell processes. An example is transport of iron ions in the protein transferrin, which is bound by corresponding receptors on the cell surface and absorbed by the cell according to the above-described mechanisms. Thus, the mathematical simulation can also be used for describing other molecular mechanisms of interaction between cells and environment by means of vesicular transport.
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REFERENCES


