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Modeling of retrograde nanoparticle transport in axons and dendrites☆

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ABSTRACT

This paper presents a pioneering modeling study on nanoparticle internalization and transport in neurons. The model developed in this paper is based on recent experimental results that indicate that after entering a neurite by endocytosis, nanoparticles are transported toward the neuron soma in endocytic vesicles by retrograde molecular-motor-driven transport. Experimental results also indicate that nanoparticles enter axons at axon terminals while in dendrites they enter through the entire plasma membrane. The model equations developed in this paper are based on these experimental observations. The analytical solution of these equations is obtained; the solution predicts the distribution of the concentration of nanoparticles associated with free nanoparticle-loaded vesicles (NLVs) (not transported on microtubules (MTs)) as well as the distribution of the concentration of nanoparticles associated with NLVs transported on MTs by dynein motors. The fluxes of nanoparticles by diffusion and motor-driven transport as well as the total (combined) flux of nanoparticles are also predicted.

1. Introduction

Nanotechnology has numerous emerging applications in medicine. Diagnostic, therapeutic, and targeting agents can be incorporated within different types of nanoparticles, such as quantum dots, liposomes, and viruses [1]. One of the advantages of nanoparticles is that, if properly designed, they are capable of penetrating various tissue barriers, such as the blood-brain barrier [2,3]. The blood-brain barrier presents the major obstacle for treatment of many brain disorders because it is difficult for many therapeutic and diagnostic agents to cross this barrier in adequate amounts. Patients with neurodegenerative conditions, such as Alzheimer's, Parkinson's, and Huntington's diseases, may benefit from novel drugs, if these drugs can be delivered to specific areas of the brain.

This paper is motivated by the recent research of Wong et al. [4] who investigated the utilization of layered double hydroxide nanoparticles for the delivery of small interfering RNAs (siRNAs) [5] to neuron bodies. Such siRNAs are capable of destroying specific messenger RNAs. This makes siRNAs suitable for treatment of such disorders as Huntington's disease, which is linked to the production of abnormal proteins. The advantages of using nanoparticles as delivery vehicles for siRNAs include the fact that they can be administered intravenously [6]; also, layered double hydroxide nanoparticles exhibit low cytotoxicity, are biocompatible, and much more efficiently internalized by cortical neurons than by many non-neuronal cell lines.

Nanoparticles most likely enter neurons by clathrin-dependent endocytosis [7]. Once they entered neurons, nanoparticles are transported toward the neuron body (where they are released into the cytoplasm) by retrograde transport in endocytic vesicles through association with dynein molecular motors [4,8,9]. Neurons have two types of long processes, axons and dendrites; axons transmit signals and dendrites receive signals. Interestingly, there is evidence that nanoparticles enter axons at axon terminals while in dendrites nanoparticles enter through the entire plasma membrane [4,10,11].

This paper develops, based on the above experimental observations, models of nanoparticle transport from their place of entry to the neuron body. Two models are developed, for an axon and a dendrite. Transport of nanoparticles in these two neuronal processes is then compared.

2. Governing equations

Fig. 1a and b shows schematic diagrams of the problem. In an axon (Fig. 1a) nanoparticles enter through the axon synapse only, where the nanoparticle concentration is assumed to be the highest. In a dendrite (Fig. 1b) nanoparticles enter along the whole length of the dendrite. After they have entered, nanoparticles are transported in nanoparticle-loaded vesicles (NLVs) retrogradely toward the neuron soma, where nanoparticle concentration is assumed to be the lowest. It is assumed that after releasing their cargo in the cell body, nanoparticles are directed to lysosomes for degradation (which provides a sink for nanoparticles in the soma); this assumption allows solving the problem in a steady-state formulation.

Equations describing nanoparticle transport are based on the model of molecular motor-assisted transport of intracellular organelles

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