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Effect of pharmaceutical agent degradation on axonal transport drug delivery: An analytical solution for a transient situation☆

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ABSTRACT

This paper is motivated by recent experimental research that demonstrated pharmacological efficiency of axonal transport drug delivery. The purpose is to develop a model of this process and to study how the rate of destruction of pharmaceutical agent complexes (PACs) affects their transport in the axon. The model includes two populations of PACs: PACs in the state when they are driven retrogradely (from the axon terminal toward the neuron soma) by dynein motors and PACs residing in the accumulated state (but can still be re-released to the dynein-driven state). The coupling between the kinetic states is accounted for by first-order reactions. Utilizing Laplace transform, analytical solutions for concentrations of these two populations of PACs are obtained. The effect of PAC destruction is investigated for different values of other parameters. It is shown that the shapes of the waves describing the PAC concentrations can be significantly affected by transport parameters.

1. Introduction

This paper is motivated by recent experimental research by Filler et al. [1] who demonstrated pharmacological efficiency of tripartite complexes that were loaded with drug molecules (up to a hundred drug molecular per one complex) and used for a targeted drug delivery by means of retrograde axonal transport. Retrograde axonal transport is powered by dynein molecular motors (this makes it possible to transport large intracellular particles) that run on microtubules (MTs) [2–7].

The results obtained by Filler et al. [1] demonstrated that during retrograde transport, a large amount of transported drug accumulated in the axon, and then was re-released. According to [1,8], the accumulation most likely occurred at the Nodes of Ranvier. This paper continues the research initiated in [9] and develops a mathematical model of axonal transport drug delivery that accounts not only for the drug accumulation in the axon, but also for its destruction during its transport toward the neuron soma. The method of obtaining an analytical solution of governing equations relies on mathematical techniques developed in [10–13].

2. Governing equations

Fig. 1a displays a schematic diagram of the problem. It is assumed that when $0<t<t_c$ the axon terminal (at $x=0$) is subjected to a constant PAC flux. When $t>t_c$ the PAC flux at the axon terminal is equal to zero. Once PACs enter the axon, they are transported by dynein motors toward the neuron soma. As they are transported, PACs can be absorbed at the Nodes of Ranvier and also they can be destroyed. Accumulated PACs can be re-released and re-enter dynein-driven transport. Thus the model includes two populations of PACs: those transported by dynein motors and those accumulated at the Nodes of Ranvier (see Fig. 1b). The presence of the population of accumulated particles makes the problem different from that considered in Smith and Simmons [14].

Since there are a large number of Nodes of Ranvier in the axon, the absorption and re-release of PACs is assumed to occur continuously along the axon length. The above assumptions result in the following system of two governing equations expressing the conservation of accumulated and dynein-driven complexes, respectively:

$$\frac{\partial n_0}{\partial t} = -kn_0 + k' n_- \tag{1}$$

$$\frac{\partial n_-}{\partial t} = kn_0 - k' n_- - v\frac{\partial n_-}{\partial x} - k_{destr} n_- \tag{2}$$

where k is the first order rate constant characterizing the rate at which PACs are re-released from the accumulated state, k' is the first order rate constant characterizing the rate at which PACs are absorbed at the Nodes of Ranvier, k_{destr} is the first order rate constant characterizing the rate of destruction of dynein-driven PACs, n_0 is the number density of PACs accumulated at a particular location in the axon, n_- is the number density of PACs transported retrogradely by dynein motors, t is the time, v is the average velocity of dynein motors, and x is the linear

Abbreviations: MT, microtubule; PAC, pharmaceutical agent complex.

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