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Modeling the effect of degradative pathway associated with Nodes of Ranvier on axonal transport drug delivery ☆

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ABSTRACT

The goal of this paper is to develop a mechanistic model of axonal transport drug delivery. The model accounts for the dynamics of transport of pharmaceutical agent complexes (\PACs) by dynein motors along microtubules (MTs) from the axon periphery toward the neuron soma, PAC accumulation in the axon, and PAC transport out of the axon via a degradative pathway that is associated with Nodes of Ranvier. The model assumes two populations of PACs: (1) PACs that are in retrograde transit propelled by dynein motors and (2) PACs accumulated at Nodes of Ranvier. The obtained governing equations describing the dynamics of these two PAC populations are transformed into dimensionless form and solved analytically utilizing Laplace transform. The obtained results reveal that for certain values of kinetic constants involved in the model the concentration of accumulated PACs can be independent of the position in the axon. To explain the obtained result this case is analyzed separately. Physical significance of computational results is discussed.

1. Introduction

Systemic side effects limit the utility of many pharmaceutical agents [1]; therefore, targeted drug delivery to selected populations of neurons has many potential advantages over systemic administration of the same drug. One possibility to achieve this goal is to use retrograde axonal transport that moves various organelles from the axon periphery toward the body of the cell (neuron soma) [2–4]. Axonal transport drug delivery [5–9] thus involves absorption of a drug at the axon synapse and then its transport to the neuron soma when a drug, loaded into PACs, is moved retrogradely by dynein motors (see Fig. 1a). Dynein motors are processive molecular motors that walk toward MT minus-ends, using MTs as railway tracks. Recently, Filler et al. [1] reported results of chemical synthesis of a tripartite complex that consisted of an axon transport facilitator molecule, a polymer linker, and a large number of drug molecules, for targeted drug delivery to neurons. According to [1], up to 100 drug molecules could be loaded per one such complex; the obtained results indicate a tenfold increase in the drug half life and a 300 fold decrease in the necessary dose compared to systemic administration.

This paper continues the effort on mechanistic modeling of axonal transport drug delivery initiated in [10–13]. In order to describe the dynamics of PAC transport, two populations of PACs are assumed: those that are moved retrogradely by dynein motors and those that accumulate at certain locations in the axon (at Nodes of Ranvier). The kinetic processes between these two populations of PACs are displayed in Fig. 1b. Accumulation is described by a first-order reaction and is characterized by a kinetic constant k_a^* (s^{-1}). According to [1], accumulation is explained by PAC endocytosis by paranodal complexes of Schwann cells at the Nodes of Ranvier. Accumulated PACs cannot move; however, according to [14], the endocytosed material can be taken out of the axon via a degradative pathway associated with Nodes of Ranvier. This degradation process is described by a first-order reaction and is characterized by a kinetic constant k_{degr}^* (s^{-1}). Also, [1] suggested that some accumulated PACs can be re-released back to the axon; this process is also described by a first-order reaction and is characterized by a kinetic constant k_r^* (s^{-1}). Compared to previous work [10–13], modeling of drug removal from the accumulated state out of the axon via a degradative pathway presented here is new; the main concentration is made on elucidating the effect of this pathway on the dynamics of axonal transport drug delivery.

2. Governing equations

A sketch of the problem is displayed in Fig. 1a. It is assumed that the axon terminal is exposed to PACs for the time t_c^*. During that time PACs enter the axon terminal at a constant rate (see Fig. 1c). After they enter, PACs are transported by dynein motors toward the neuron soma.

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Nomenclature

$H(\eta)$	Heaviside step function
$I_1(\eta)$	modified Bessel function of the first kind of order 1
j^*	flux of \PACs (driven by dynein motors) (1/μm^{2}s)
j_0^*	PAC flux at the axon terminal during the exposure (see Fig. 1c) (1/μm^{2}s)
k_a^*	first order rate constant characterizing the rate at which PACs are absorbed at the Nodes of Ranvier (1/s)
k_{degr}	dimensionless value of k_{degr}^*, k_{degr}^*/k_a^*
k_{degr}^*	first order rate constant characterizing the rate at which PACs that are absorbed at the Nodes of Ranvier are degraded and taken out of the axon (s^{-1})
k_r	dimensionless value of k_r^*, k_r^*/k_a^*
k_r^*	first order rate constant characterizing the rate at which PACs are re-released from the accumulated state (1/s)
n_a	dimensionless value of n_a^*, $n_a^* v^*/j_0^*$
n_a^*	number density of PACs accumulated at a particular location in the axon (1/μm^3)
n_-	dimensionless value of n_-^*, $n_-^* v^*/j_0^*$
n_-^*	number density of PACs transported retrogradely by dynein motors (1/μm^3)
n_{total}	$n_a + n_-$
$N_a(x, s)$	Laplace transform of the function $n_a(x, t)$
$N_-(x, s)$	Laplace transform of the function $n_-(x, t)$
t	dimensionless time, $t^* k_a^*$
t^*	time (s)
t_c	dimensionless duration of the PAC exposure, $t_c^* k_a^*$
t_c^*	duration of the PAC exposure (s)
v^*	average velocity of dynein motors (μm/s)
x	dimensionless linear coordinate, $x^* k_a^*/v^*$
x^*	linear coordinate that starts at the axon terminal and is directed toward the neuron soma, see Fig. 1a (μm)

Kinetic processes between the two populations of PACs described above are shown in Fig. 1b. The continuum approach to intracellular transport is utilized [15]. Also, it is assumed that due to a large number of the Nodes of Ranvier, the discrete spacing of the Nodes of Ranvier can be neglected and it is assumed that PACs are continuously absorbed and then re-released along the axon length. This assumption is reasonable, given that the spacing of the Nodes of Ranvier is ~100 μm while drug delivery problems typically involve distances ~1 cm. Under these assumptions, equations describing the conservation of the two populations of PACs are

$$\frac{\partial n_a^*}{\partial t^*} = -k_r^* n_a^* + k_a^* n_-^* - k_{degr}^* n_a^* \tag{1}$$

$$\frac{\partial n_-^*}{\partial t^*} = k_r^* n_a^* - k_a^* n_-^* - v^* \frac{\partial n_-^*}{\partial x^*} \tag{2}$$

where n_a^* is the number density of PACs accumulated at a particular location in the axon (1/μm^3); n_-^* is the number density of PACs transported retrogradely by dynein motors (1/μm^3); t^* is the time (s); v^* is the average velocity of dynein motors (μm/s); and x^* is the linear coordinate that starts at the axon terminal and is directed toward the neuron soma (μm), see Fig. 1a. Asterisks denote dimensional variables. Eq. (1) expresses the conservation of PACs accumulated in the axon while Eq. (2) expresses the conservation of PACs that are transported by dynein motors. These two equations are coupled through the kinetic terms that describe transitions between these two populations of PACs (see Fig. 1b).

Since PACs are assumed to be driven by dynein motors, their flux, measured in 1/μm^{2}s, is given by

$$j^* = v^* n_-^* \tag{3}$$

The boundary condition at $x^* = 0$ is

$$j^*(0, t^*) = v^* n_-^*(0, t^*) = j_0^*[1 - H(t^* - t_c^*)] \tag{4}$$

where $H(\eta)$ is the Heaviside step function; j_0^* is the PAC flux at the axon terminal during the exposure (1/μm^{2}s), see Fig. 1c; and t_c^* is the duration of the PAC exposure (s). It is assumed that the neuron soma acts as a perfect absorber of PACs (no wave reflection at the axon hillock [16]), which means that the solution can be obtained assuming a semi-infinite domain, $x^* \in [0, \infty)$.

It is assumed that at $t^* = 0$ there are no PACs in the axon, $n_a^*(x^*, 0) = 0$ and $n_-^*(x^*, 0) = 0$.

The dimensionless forms of Eqs. (1) and (2) are

$$\frac{\partial n_a}{\partial t} = -k_r n_a + n_- - k_{degr} n_a \tag{5}$$

$$\frac{\partial n_-}{\partial t} = k_r n_a - n_- - \frac{\partial n_-}{\partial x} \tag{6}$$

where the dimensionless variables are defined as follows:

$$x = \frac{x^* k_a^*}{v^*},\ n_a = n_a^* \frac{v^*}{j_0^*},\ n_- = n_-^* \frac{v^*}{j_0^*},\ t = t^* k_a^* \tag{7}$$

and the dimensionless kinetic constants are defined as

$$k_r = \frac{k_r^*}{k_a^*}, \quad k_{degr} = \frac{k_{degr}^*}{k_a^*} \tag{8}$$

The dimensionless form of boundary condition (4) is

$$n_-(0, t) = 1 - H(t - t_c) \tag{9}$$

where

$$t_c = t_c^* k_a^* \tag{10}$$

Eqs. (5) and (6) with boundary condition (9) and zero initial conditions (it is assumed that initially there were no PACs in the axon) are solved by Laplace transform. The subsidiary equations are

$$sN_a = -k_r N_a + N_- - k_{degr} N_a \tag{11}$$

$$sN_- = k_r N_0 - N_- - \frac{\partial N_-}{\partial x} \tag{12}$$

where $N_a(x, s)$ and $N_-(x, s)$ are the Laplace transforms of the functions $n_a(x, t)$ and $n_-(x, t)$, respectively.

The Laplace transform of boundary condition (9) is

$$N_-(0, s) = \frac{1 - e^{-s t_c}}{s} \tag{13}$$

The solutions of subsidiary Eqs. (11) and (12) subject to boundary condition (13) are

$$N_a(x, s) = \frac{1 - \exp[-s t_c]}{s\left(k_{degr} + k_r + s\right)} \exp\left[-x - sx + \frac{k_r x}{k_{degr} + k_r + s}\right] \tag{14}$$