Mathematical Biosciences 253 (2014) 19–24

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

What tau distribution maximizes fast axonal transport toward the axonal synapse?

I.A. Kuznetsov [a], A.V. Kuznetsov [b,*]

[a] Dept. of Biomedical Engineering, Johns Hopkins University, Baltimore, MD 21218-2694, USA
[b] Dept. of Mechanical and Aerospace Engineering, North Carolina State University, Raleigh, NC 27695-7910, USA

ARTICLE INFO

Article history:
Received 4 December 2013
Received in revised form 19 March 2014
Accepted 4 April 2014
Available online 18 April 2014

Keywords:
Tau protein
Organelle transport
Optimal control
Alzheimer's disease

ABSTRACT

This theoretical research is aimed at investigating the question of why tau protein concentration exhibits a proximal–distal increase in healthy axons and a proximal–distal decrease in degenerating axons in Alzheimer's disease. We developed a model of fast axonal transport toward the axon synapse. The model is based on recently published experimental results by Dixit et al. (2008) [1] who reported that the attachment rate of kinesin-1 to MTs is reduced by tau. Cytoplasmic dynein is affected less by tau (dynein is affected at much higher tau concentrations than those that affect kinesin-1). We used the model to investigate the effect of various tau distributions along the axon length on organelle flux toward the axon synapse. We found that a proximal–distal increase in tau concentration leads to a higher organelle flux while a proximal–distal decrease in tau concentration leads to a smaller organelle flux than a uniform tau concentration. We also computed what tau distribution would give the largest organelle flux toward the synapse. We found that in order to maximize organelle flux, the tau concentration has to be at its minimum level in the proximal axon and its maximum level at the distal axon, which is in agreement with the bang–bang principle in optimal control theory.

1. Introduction

Tau is a microtubule(MT)-associated protein found in neurons (Peter and Mofrad [2], Conde and Caceres [3]). In axons, tau has many functions that include regulation of MT stability and synaptic functions (Morris et al. [4]). Recent interest in tau is to a large degree due to evidence implicating tau dysfunction in Alzheimer's disease (AD). In AD, most of tau detaches from MTs. The large cytosolic concentration of free tau and increased tau phosphorylation increase the probability of tau conversion into its neurotoxic forms (Ballatore et al. [5]). A hallmark of AD is tau aggregates called neurofibrillary tangles (NFTs) (Cohen et al. [6], Selkoe [7]). Recent data also suggest neurotoxicity of tau oligomers, which are soluble species of tau that are intermediates between tau monomers and NFTs (Gerson and Kayed [8], Lasagna-Reeves et al. [9]).

Another function of tau that may be possibly related to AD is its effect on regulating intracellular traffic in axons. One reason for axon degeneration in AD may be the deficit of organelle transport toward the axon synapse (Stokin et al. [10]). Indeed, data reported in Ebneth et al. [11], Stamer et al. [12], and Xu et al. [13] support the notion that tau retards kinesin-driven transport along MTs. A possible mechanism is that tau occupies MT binding sites thus making it more difficult for kinesin to bind to MTs. Vershinin et al. [14] investigated, in vitro, the situation when cargo is moved by several kinesin motors. They demonstrated that by blocking kinesin from reattaching to an MT, tau can reduce the number of kinesin motors that drive the cargo. Dixit et al. [1] reported that the attachment rate of kinesin-1 to MTs is reduced by tau. The effect of tau on cytoplasmic dynein is smaller (tau concentration that affects dynein is 10-fold higher that the concentration that affects kinesin-1).

It should be noted that tau's role in traffic regulation in axons is not without controversy. Results reported by Morfini et al. [15] and Yuan et al. [16] suggest that tau binding to MTs does not affect kinesin or dynein motilities. A possible explanation is that the ability of tau to inhibit kinesin-driven transport depends on the mode of tau interaction with MTs (McVicker et al. [17]) and on a particular tau isoform (Vershinin et al. [14]).

Most of the tau in a healthy cell is bound to MTs (Morris et al. [4]). The distribution of the MT-bound tau in healthy axons exhibits a proximal–distal increase (Kempf et al. [18], Mandell and Banker [19]). However, in AD tau accumulates in neuron soma, causing a proximal–distal decreasing tau distribution (Dixit et al. [1]).

* Corresponding author. Tel.: +1 919 515 5292.
E-mail addresses: ikuznet1@jhu.edu (I.A. Kuznetsov), avkuznet@ncsu.edu (A.V. Kuznetsov).

http://dx.doi.org/10.1016/j.mbs.2014.04.001
0025-5564/

In this paper we attempt to answer whether tau distributions observed in healthy and degenerating axons may influence organelle transport from the neuron soma to the axon synapse. We rely on data reported in Dixit et al. [1] to develop a mathematical model that gives the organelle flux toward the synapse as a function of tau distribution in the axon. We then investigate various tau distributions, including an experimentally measured one, reported in Black et al. [20]. We also solve the optimal control problem to find the tau distribution that would maximize tau transport toward the synapse and compare it with the physiological tau distribution in healthy axons.

2. Mathematical model

We assume that the attachment rate of kinesin to MTs is reduced by tau (Dixit et al. [1]). We also rely on experimental results obtained by Seitz et al. [21] who reported that tau (as well as other MAPs) reduces the attachment frequency of kinesin motors, but once the kinesin motors are attached, their speed and their run-length are not affected by the presence of tau. Since tau affects dynein only when tau concentration is very high, the effect of tau on dynein was neglected.

We used the simplest linear correlation to describe the dependence of the kinetic constant describing the rate of kinesin attachment to MTs, k_+^*, on the dimensionless tau concentration, u:

$$k_+^* = k_{+0}^*(1 - au), \tag{1}$$

where k_{+0}^* is the attachment rate to MTs for kinesin-driven organelles for the uniform ($u = 0$) tau distribution (s^{-1}) and a is a dimensionless parameter that characterizes by how much the increase of tau concentration reduces the probability of attachment of kinesin motors to MTs. Since, on physical grounds, k_+^* is non-negative, the value of a must be less than or equal to 1 (we used $a = 0.02$).

In Eq. (1)

$$u = \frac{2c^* - c_{\max}^* - c_{\min}^*}{c_{\max}^* - c_{\min}^*}, \tag{2}$$

where c^* is the concentration of tau protein per unit length of the axon (1/μm). Thus u can be interpreted as a dimensionless deviation of tau concentration from its average value. The range of u is from -1, which corresponds to the minimum tau concentration ($c_{\min}^*$) to 1, which corresponds to the maximum tau concentration ($c_{\max}^*$). This means that

$$u \in [-1, 1]. \tag{3}$$

We also assumed that the average tau concentration in the axon remains the same, only its distribution can change:

$$\int_0^{L^*} u\, dx^* = 0. \tag{4}$$

where L^* is the length of the axon (μm).

In order to quantify organelle transport toward the synapse, we characterized the organelle concentration in a particular kinetic state by the linear number density, which is the number of organelles residing in a particular kinetic state per unit length (1/μm). We considered three organelle concentrations: the concentration of free organelles, n_0^*; the concentration of MT-bound organelles driven anterogradely by kinesin motors, n_+^*; and the concentration of MT-bound organelles driven retrogradely by dynein motors, n_-^*. To obtain dimensionless concentrations, we scaled all concentrations with respect to the concentration of free organelles at $x^* = 0$, N_0^*:

$$n_0 = \frac{n_0^*}{N_0^*}, \quad n_+ = \frac{n_+^*}{N_0^*}, \quad n_- = \frac{n_-^*}{N_0^*}. \tag{5}$$

We modeled organelle distributions in the axon (see Fig. 1) by using equations of motor-assisted transport of intracellular particles suggested by Smith and Simmons in [22]. We also utilized Eq. (1) for k_+^*; all other kinetic constants were assumed to be independent of tau concentration. The unsteady versions of governing equations are given in Appendix A; for a steady-state situation these equations become:

$$-D_0^* \frac{d^2 n_0}{dx^{*2}} = -k_{+0}^*(1 - au)n_0 - k_-^* n_0 + k_+'^* n_+ + k_-'^* n_-, \tag{6}$$

$$v_+^* \frac{dn_+}{dx^*} = k_{+0}^*(1 - au)n_0 - k_+'^* n_+, \tag{7}$$

$$-v_-^* \frac{dn_-}{dx^*} = k_-^* n_0 - k_-'^* n_-, \tag{8}$$

where D_0^* is the diffusivity of free organelles (μm^2/s); v_+^* is the velocity of organelles transported by kinesin motors (μm/s); v_-^* is the velocity of organelles transported by dynein motors (μm/s); k_-^* is the attachment rate to MTs for dynein-driven organelles (s^{-1}); $k_+'^*$ is the detachment rate from MTs for kinesin-driven organelles (s^{-1}); $k_-'^*$ is the detachment rate from MTs for dynein-driven organelles (s^{-1}); and x^* is the linear coordinate along the axon (μm).

The total dimensionless organelle concentration is found as:

$$n_t(x) = n_0(x) + n_+(x) + n_-(x). \tag{9}$$

The total organelle flux, which includes the diffusion-driven, kinesin-driven and dynein-driven components, respectively, is calculated as:

$$j^* = -D_0^* \frac{dn_0^*}{dx^*} + v_+^* n_+^* - v_-^* n_-^*. \tag{10}$$

The total dimensionless organelle flux is then found as:

$$j = \frac{j^*}{v_+^* N_0^*}. \tag{11}$$

Since the problem is steady-state, j is independent of x^*. This fact can be obtained by adding Eqs. (6)–(8) and integrating the result with respect to x^*.

Eqs. (6)–(8) must be solved subject to the following boundary conditions:

$$n_0(0) = 1, \quad n_0(L^*) = N_L, \quad n_+(0) = \sigma_0, \quad n_-(L^*) = \sigma_L N_L, \tag{12}$$

where

$$N_L = \frac{N_L^*}{N_0^*}, \tag{13}$$

N_L^* is the concentration of free organelles at $x^* = L^*$; σ_0 and σ_L are the degrees of loading of free organelles on MTs at the axon hillock and at the axon tip, respectively; and N_L^* is the concentration of free organelles at $x^* = L^*$.

Our goal is to investigate how the deviation of tau concentration from its average value affects the total flux of organelles toward the axon tip.

3. The optimal control problem

We are looking for an optimal tau distribution $\hat{u}(x^*)$ that maximizes the flux of organelles toward the axon tip:

$$j = -\frac{D_0^*}{v_+^*}\frac{\partial n_0}{\partial x^*} + n_+ - \frac{v_-^*}{v_+^*} n_- \to \max. \tag{14}$$

Since j is independent of x^*, it can be evaluated, for example, at $x^* = 0$.