International Journal of Heat and Mass Transfer 51 (2008) 5695–5699

Contents lists available at ScienceDirect

International Journal of Heat and Mass Transfer

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

Modeling traffic jams in intracellular transport in axons

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ARTICLE INFO

Article history:
Received 15 November 2007
Received in revised form 4 April 2008
Available online 6 June 2008

Keywords:
Molecular motors
Motor-assisted transport
Neurons
Axons and dendrites
Intracellular organelles
Traffic jams

ABSTRACT

Irregularities in intracellular traffic in axons caused by mutations of molecular motors may lead to "traffic jams", which often result in swelling of axons causing various neurodegenerative diseases. The purpose of this paper is to suggest a model of the formation of traffic jams in axons during molecular-motor-assisted transport of intracellular organelles utilizing transport equations developed in Smith and Simmons [D.A. Smith, R.M. Simmons, Models of motor-assisted transport of intracellular particles, Biophys. J. 80 (2001) 45–68], which describe the motion of intracellular particles under the combined action of diffusion and motor-driven transport. According to this model, large intracellular organelles are transported in the cytoplasm by a combined action of diffusion and motor-driven transport. In an axon, organelles are transported away from the neuron's body toward the axon's terminal by kinesin-family molecular motors running on tracks composed by microtubules; old and used components are carried back toward neuron's body by dynein-family molecular motors. Binding/detachment kinetic processes between the organelles and microtubules are specified by first rate reaction constants; these lead to coupling between the three organelle concentrations.

1. Introduction

Neurons are highly specialized cells that have long arms (processes). If the arm transmits electrical signals, it is called an axon, whereas if it receives electrical signals, it is called a dendrite (Fig. 1) [1]. Axons in a human body can be up to one meter in length. Axons support little synthesis of proteins or membrane, therefore materials must be constantly imported from the synthetically active cytoplasm of the cell body ([2]) and transported to arms' terminals. Diffusion is not a sufficiently fast mechanism for transporting large intracellular particles (organelles), such as large protein particles or intracellular vesicles carrying different types of cargo. This is because according to Einstein's relation that determines the diffusivity of small particles due to the Brownian motion, the diffusivity is inversely proportional to the particles' radius, which means that larger particles have smaller diffusivity. To overcome the diffusion limitation, intracellular transport in axons and dendrites relies on the "railway system": large intracellular particles attach themselves to molecular motors (specialized proteins that as a result of a chemical process, usually ATP hydrolysis, undergo conformational changes "walking" along intracellular filaments, such as microtubules) that transport them along microtubules.

All microtubules (MT) in an axon have the same polarity (their plus ends point toward the axon terminal); the microtubules do not stretch the entire length of the axon so that the continuous path along the axon is composed by short overlapping segments of parallel microtubules. Transport vesicles loaded with specific proteins are carried away from the neuron body toward the synapse (the axon terminal) by kinesin-family molecular motors (this family of molecular motors is responsible for the transport on microtubules toward their plus-ends). Used and old intracellular organelles are carried from the axon terminal toward the body of the neuron by dynein-family molecular motors (this family of molecular motors is responsible for the transport on microtubules toward their minus-ends). In dendrites the microtubule polarities are mixed; some of them point their plus ends toward the dendrite tip and some point those toward the neurons' body. Therefore, in a dendrite, depending on the polarity of a particular microtubule, transport in a certain direction (to the neuron's body or away from it) can be carried out by either kinesin or dynein molecular motors ([1,3]).

Irregularities in intracellular traffic in axons caused by mutations of molecular motors may lead to "traffic jams", which may result in swelling of axons causing various neurodegenerative diseases ([2,4,5]). Hurd and Saxton [2] published electron micrographs of cross-sections through axonal swellings. The micrographs show that the swellings, caused by traffic jams induced by a mutation of a gene encoding the force-producing heavy chain of the kinesin molecular motor, are packed with mitochondria, large multi-vesicular bodies, and other types of intracellular organelles.

The purpose of this paper is to suggest a model of the formation of traffic jams in axons during molecular-motor-assisted transport

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doi:10.1016/j.ijheatmasstransfer.2008.04.022

Nomenclature

D_0	dimensionless diffusivity of a free particle, $\frac{\widetilde{D}_0\tilde{k}_+}{\tilde{v}_+^2}$
$\widetilde{D}_0$	diffusivity of a free particle
k_-	dimensionless binding rate to microtubules for particles that move in the negative direction, $\frac{\tilde{k}_-}{\tilde{k}_+}$
$\tilde{k}_\pm$	first order rate constants for binding to microtubules for particles that move in the positive (+) and negative (−) directions, respectively
$k'_\pm$	dimensionless detachment rate from microtubules for particles that move in the positive (+) and negative (−) directions, respectively, $\frac{k'_\pm}{\tilde{k}_+}$
$k'_{\pm 0}$	dimensionless detachment rate from microtubules for particles that move in the positive (+) and negative (−) directions for the case when concentration of particles riding on microtubules is very low
$\tilde{k}'_\pm$	first order rate constants for detachment from microtubules for particles that move in the positive (+) and negative (−) directions, respectively
L	dimensionless axon length, $\frac{\widetilde{L}\tilde{k}_+}{\tilde{v}_+}$
$\widetilde{L}$	axon length
n_0	dimensionless free particle concentration, $\tilde{n}_0\frac{\tilde{v}_+^3}{\tilde{k}_+^3}$
$\tilde{n}_0$	free particle concentration
$n_\pm$	dimensionless concentration of particles moving on microtubules in the positive (+) and negative (−) directions, respectively, $\tilde{n}_\pm\frac{\tilde{v}_+^3}{\tilde{k}_+^3}$
$\tilde{n}_\pm$	concentration of particles moving on microtubules in the positive (+) and negative (−) directions, respectively
N_0	dimensionless concentration of free particles maintained at $x = 0$, $\widetilde{N}_0\frac{\tilde{v}_+^3}{\tilde{k}_+^3}$
$\widetilde{N}_0$	constant concentration of free particles maintained at $\tilde{x} = 0$
N_L	dimensionless concentration of free particles maintained at $x = L$, $\widetilde{N}_L\frac{\tilde{v}_+^3}{\tilde{k}_+^3}$
$\widetilde{N}_L$	constant concentration of free particles maintained at $\tilde{x} = \widetilde{L}$
$\tilde{t}$	time
v_-	dimensionless velocity of a particle moving on a microtubule toward the cell body, $\frac{\tilde{v}_-}{\tilde{v}_+}$
v_{-0}	dimensionless velocity of a particle moving on a microtubule in the negative (−) direction for the case when concentration of particles riding on microtubules is very low
$\tilde{v}_\pm$	velocity of a particle moving on a microtubule in the positive (+) and negative (−) directions, respectively
x	dimensionless particle displacement in the axon, $\frac{\tilde{x}\tilde{k}_+}{\tilde{v}_+}$
$\tilde{x}$	particle displacement in the axon

Greek symbols

σ_0	degree of loading at $\tilde{x} = 0$
σ_L	degree of loading at $\tilde{x} = \widetilde{L}$

of intracellular organelles utilizing transport equations developed in Smith and Simmons [6] which describe motion of intracellular particles under the combined action of diffusion and motor-driven transport. According to this model, the organelle either diffuses freely in the cytosol or moves on a filament at a motor velocity; the organelle can bind to or detach from a filament. Depending on the type of a molecular motor (or several motors) attached to the particle, the motion along the microtubule can occur in either direction. Dinh et al. [7] presented numerical solutions of Smith–Simmons equations to describe intracellular trafficking of adenoviruses between the cell membrane and cell nucleus. Other relevant aspects of intracellular transport of cell organelles and vesicles along microtubules are considered in [8–15].

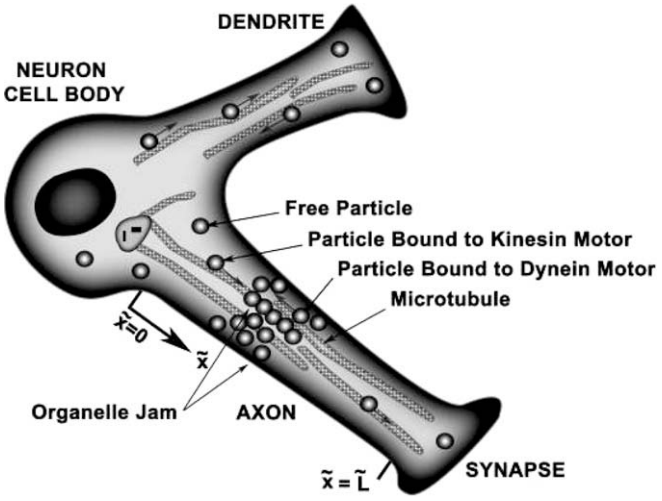

Fig. 1. Schematic diagram of a neuron cell with a dendrite and axon; also, a traffic jam in the axon resulting from crowding of organelles at a certain location in the axon.

2. Governing equations

The molecular-motor-assisted transport equations suggested in Smith and Simmons [6] are

$$\frac{\partial\tilde{n}_0}{\partial\tilde{t}} = \widetilde{D}_0\frac{\partial^2\tilde{n}_0}{\partial\tilde{x}^2} - (\tilde{k}_+ + \tilde{k}_-)\tilde{n}_0 + \tilde{k}'_+\tilde{n}_+ + \tilde{k}'_-\tilde{n}_- \tag{1}$$

$$\frac{\partial\tilde{n}_+}{\partial\tilde{t}} = \tilde{k}_+\tilde{n}_0 - \tilde{k}'_+\tilde{n}_+ - \frac{\partial(\tilde{v}_+\tilde{n}_+)}{\partial\tilde{x}} \tag{2}$$

$$\frac{\partial\tilde{n}_-}{\partial\tilde{t}} = \tilde{k}_-\tilde{n}_0 - \tilde{k}'_-\tilde{n}_- - \frac{\partial(\tilde{v}_-\tilde{n}_-)}{\partial\tilde{x}} \tag{3}$$

where $\widetilde{D}_0$ is the diffusivity of a free particle; $\tilde{t}$ is the time; $\tilde{n}_0$ is the free particles concentration; $\tilde{n}_+$ is the concentration of particles moving on microtubules in the positive direction (away from the cell body); $\tilde{n}_-$ is the concentration of particles moving on microtubules in the negative direction (toward the cell body); $\tilde{x}$ is the linear coordinate along the axon; $\tilde{v}_-$ is the velocity of a particle moving on a microtubule toward the cell body (in an axon this is the motor velocity generated by a dynein-family molecular motor), $\tilde{v}_-$ is negative; $\tilde{v}_+$ is the velocity of a particle moving on a microtubule away from the cell body (in an axon this is the motor velocity generated by a kinesin-family molecular motor), $\tilde{v}_+$ is positive; $\tilde{k}_+$ and $\tilde{k}_-$ are the first order rate constants for binding to microtubules for particles that move in the positive and negative directions, respectively; and $\tilde{k}'_+$ and $\tilde{k}'_-$ are the first order rate constants for detachment from microtubules for particles that move in the positive and negative directions, respectively. Eqs. (1)–(3) to be solved subject to the following boundary conditions:

$$\tilde{x} = 0, \quad \tilde{n}_0 = \widetilde{N}_0, \quad \tilde{n}_+ = \sigma_0\widetilde{N}_0 \tag{4}$$

$$\tilde{x} = \widetilde{L}, \quad \tilde{n}_0 = \widetilde{N}_L, \quad \tilde{n}_- = \sigma_L\widetilde{N}_L \tag{5}$$