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Modeling neuropeptide transport in various types of nerve terminals containing en passant boutons

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ABSTRACT

We developed a mathematical model for simulating neuropeptide transport inside dense core vesicles (DCVs) in axon terminals containing en passant boutons. The motivation for this research is a recent experimental study by Levitan and colleagues (Bulgari et al., 2014) which described DCV transport in nerve terminals of type Ib and type III as well as in nerve terminals of type Ib with the transcription factor DIMM. The goal of our modeling is validating the proposition put forward by Levitan and colleagues that the dramatic difference in DCV number in type Ib and type III terminals can be explained by the difference in DCV capture in type Ib and type III boutons rather than by differences in DCV anterograde transport and half-life of resident DCVs. The developed model provides a tool for studying the dynamics of DCV transport in various types of nerve terminals. The model is also an important step in gaining a better mechanistic understanding of transport processes in axons and identifying directions for the development of new models in this area.

1. Introduction

Neuropeptide molecules are important for regulating mood, behavior, and development [1–3]. Neuropeptides are often released simultaneously with neurotransmitters, but unlike neurotransmitters, neuropeptides are synthesized in the neuron soma [4,5] and delivered toward axon terminals in dense-core vesicles (DCVs) by means of fast axonal transport [6–9]. Anterograde motion of DCVs is driven by kinesin (KIF1A) molecular motors [10] and retrograde motion of DCVs is believed to be driven by dynein motors [11–13].

Many nerve terminals contain en passant boutons (hereafter boutons), sequential varicose sites that serve to accumulate and release neuropeptides and neurotransmitters [14,15]. Nerve terminals may differ by the type of boutons that they contain. In this paper we are interested in modeling DCV transport in Drosophila motor neurons. In particular, we are interested in simulating the difference in DCV transport in nerve terminals that contain type Ib and type III boutons. We are also interested in investigating the effect that the transcription factor Dimmed (DIMM) [16,17] has on DCV accumulation and transport in nerve terminals that contain type Ib boutons.

Morphology of type Ib axon terminals is described in [18] and morphology of type Ib and type III axon terminals is described in [19]. Levitan and coworkers [20] found that in nerve terminals with type Ib boutons most anterogradely moving DCVs pass a proximal bouton (only about 10% of them are captured). The DCVs initially accumulate in the most distal bouton. The excess DCVs (those not captured in the most distal bouton) then leave the most distal bouton by retrograde transport and return to the proximal axon. In the proximal axon the DCVs turn again and re-enter the axon terminal, thus forming a circulation between the proximal axon and the most distal bouton.

The picture is drastically different in nerve terminals with type III boutons. In these terminals DCVs initially accumulate in the proximal boutons with little DCV flux reaching the most distal bouton. As DCVs pass a proximal bouton, about 65% of them are captured [21].

Bulgari et al. [21] reported that the DCV fluxes entering the nerve terminals with type Ia and type III boutons are approximately the same. Half-life of DCVs in these two types of boutons is also approximately the same (~6 h). Bulgari et al. [21] explained the difference in neuropeptide accumulation by the difference in DCV capture in these different types of boutons. Our goal is to develop a mathematical model that would enable a simulation of DCV transport in these two types of nerve terminals. Our original model of DCV transport in nerve terminals with type Ib boutons was reported in [22]. Here we revised the model significantly and generalized it to include transport in nerve terminals with type III boutons.

It is known that DIMM makes type Ib boutons more similar to type III boutons [21]. Bulgari et al. [21] explained this by the fact that DIMM increases the capture efficiency of DCVs in type Ib boutons. We used our new mathematical model to test this hypothesis. In particular, we

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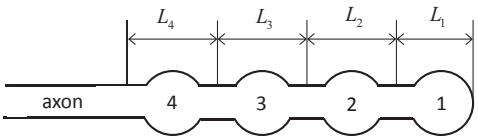

Fig. 1. Schematic diagram of a nerve terminal with four en passant boutons. The boutons are numbered as in [20].

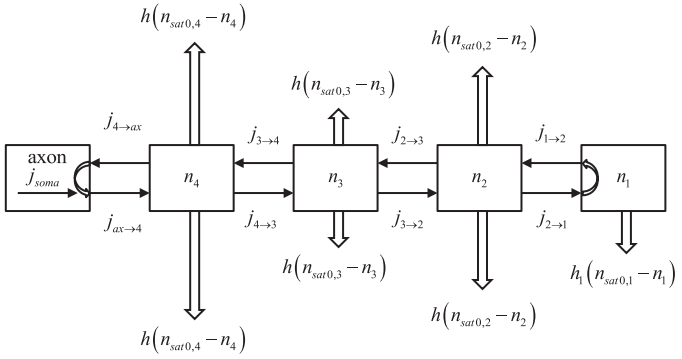

Fig. 2. Kinetic diagram showing DCV fluxes between the axonal compartment and four en passant boutons. DCV fluxes between the compartments ($j_{ax\to4}$, $j_{4\to3}$, etc.) and fluxes resulting from the capture of DCVs in the boutons ($h(n_{sat0,4}-n_4)$, $h(n_{sat0,3}-n_3)$, etc.) are also displayed.

tested whether the increase of DCV capture efficiency would result in the switch from distal to proximal recovery in type Ib boutons, an experimental observation that is reported in Fig. 4C of [21].

2. Materials and models

2.1. Governing equations

Fig. 1 displays a sketch of the problem. A neuron terminal which contains four boutons is simulated. The boutons are numbered the same way as in [20]. Fig. 2 displays DCV fluxes between the axonal compartment and four boutons; these fluxes are shown by regular arrows. Fluxes resulting from DCV capture in boutons are displayed by block arrows.

The following assumptions concerning the DCV fluxes were made in the model:

(i) The rate of DCV capture in a bouton is proportional to the difference between the saturated (steady-state) DCV concentration at infinite DCV half-life and the current concentration of resident DCVs in the bouton.
(ii) The DCV flux from the axonal compartment to bouton 4, $j_{ax\to4}$, is constant.
(iii) An anterograde DCV flux leaving a bouton compartment is calculated as the DCV flux entering the compartment minus the rate of DCV capture in this compartment.
(iv) Since DCVs have to switch molecular motors from kinesin to dynein in bouton 1 to continue their journey, we assumed that the retrograde flux leaving bouton 1 is delayed by 300 s, the time needed to switch from kinesin to dynein motors.
(v) Retrogradely moving DCVs not captured in bouton 4 return to the axonal compartment where they may switch from dynein to kinesin motors and re-enter the circulation.

Model variables are listed in Table 1 and model parameters are listed in Table 2.

Various DCV concentrations (see Tables 1 and 2) are characterized by their linear number density, which is the number of DCVs residing in a particular compartment (bouton) per unit length of that compartment. The DCV concentration in the resident state is determined by the balance between DCV capture and loss in the resident state (the loss occurs due to a finite DCV half-life in the resident state). Even at steady-state the rate of DCV capture cannot be zero because DCV capture must compensate for DCV loss in the resident state. For this reason, in defining the driving potential for DCV capture we used the DCV saturated concentrations at infinite DCV half-life, $n_{sat0,i}$ ($i=1,\ldots,4$). $n_{sat0,i}$ is larger than the actual saturated concentration of DCVs, $n_{sat,i}$. In this formulation even at steady-state the value of the difference $n_{sat0,i}-n_{sat,i}$ is positive. This insures that DCV capture continues at steady state, which is necessary to compensate for DCV loss in the resident state. The concentrations of DCVs residing in the four boutons are then found from the following conservation equations, respectively:

$$L_1\frac{dn_1}{dt}=h_1(n_{sat0,1}-n_1)-L_1\frac{n_1\ln(2)}{T_{1/2}}, \tag{1}$$

$$L_2\frac{dn_2}{dt}=h_2(n_{sat0,2}-n_2)+H[\tilde{j}_{1\to2}]H[t-t_1]h_2(n_{sat0,2}-n_2)-L_2\frac{n_2\ln(2)}{T_{1/2}}, \tag{2}$$

$$L_3\frac{dn_3}{dt}=h_3(n_{sat0,3}-n_3)+H[\tilde{j}_{2\to3}]H[t-t_1]h_3(n_{sat0,3}-n_3)-L_3\frac{n_3\ln(2)}{T_{1/2}}, \tag{3}$$

$$L_4\frac{dn_4}{dt}=h_4(n_{sat0,4}-n_4)+H[\tilde{j}_{3\to4}]H[t-t_1]h_4(n_{sat0,4}-n_4)-L_4\frac{n_4\ln(2)}{T_{1/2}}, \tag{4}$$

where H is the Heaviside step function. The term $H[\tilde{j}_{1\to2}]$ in Eq. (2) describes the fact that DCVs can be captured during their retrograde transport only if there is a positive retrograde DCV flux entering

Table 1
Model variables.

Symbol	Definition	Units
t	Time	[s]
$n_1(t)$, $n_2(t)$, $n_3(t)$, $n_4(t)$	Concentrations of resident DCVs in boutons 1, 2, 3, and 4, respectively	[vesicles/μm]
$j_{a\to b}(t)$	Flux of DCVs from compartment "a" to compartment "b" (see Fig. 2)	[vesicles/s]

Table 2
Model parameters.

Symbol	Definition	Units
h_1, h_2, h_3, h_4	Mass transfer coefficients characterizing the rates of DCV capture in boutons 1, 2, 3, and 4, respectively	[μm/s]
$j_{ax\to4}$	Flux from the axonal compartment to the most proximal bouton	[vesicles/s]
L_1, L_2, L_3, L_4	Lengths of compartments occupied by boutons 1, 2, 3, and 4, respectively, see Fig. 1	[μm]
$n_{sat0,1}$, $n_{sat0,2}$, $n_{sat0,3}$, $n_{sat0,4}$	Saturated concentrations of DCVs in boutons 1, 2, 3, and 4, respectively, at infinite DCV half-life	[vesicles/μm]
t_1	Time that it takes for vesicles to change direction in the most distal bouton, if they are not captured (we used $t_1=300$ s)	[s]
$T_{1/2}$	Half-life of resident DCVs	[s]