Simulating the effect of formation of amyloid plaques on aggregation of tau protein

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Supplementary Material

S1. Tables

Table S1. Independent variables in the models of APP and tau transport.

Symbol	Definition	Units
x^*	Cartesian coordinate along the axon	μm
t^*	Time	s

Table S2. Dependent variables in the model of APP transport.

Symbol	Definition	Units
c_+^*	Linear number density of anterogradely transported APP molecules in the axon	μm^{-1}
c_-^*	Linear number density of retrogradely transported APP molecules in the axon	μm^{-1}
c_0^*	Linear number density of free APP molecules in the axon (not actively transported by motors on MTs)	μm^{-1}
$c_{A\beta,ax}^*$	Linear number density of extracellular amyloid-β polymers originating from the axon	μm^{-1}
C_s^*	Number of APP molecules in the soma	

$C^*_{A\beta,ax}$	Number of extracellular amyloid-β polymers originating from the axon	
$C^*_{A\beta,s}$	Number of extracellular amyloid-β polymers originating from the soma	
$C^*_{A\beta,tot}$	Total number of extracellular amyloid-β polymers originating from the axon and from the soma	
j^*_{APP}	Flux of APP molecules	s^{-1}

Table S3. Parameters characterizing APP transport and their estimated values.

Symbol	Definition	Units	Estimated value	Reference or estimation method
$C^*_{s,i}$	Initial number of APP molecules in the soma		7.932×10^{5} [a]	Eqs. (13) and (14)
h^*_{APP}	Mass transfer coefficient characterizing transport of APP from the soma to the axon	s^{-1}	5.835×10^{-5} [a]	Eqs. (13) and (14)
$k^*_{1,ax}$	Rate constant for the first pseudoelementary step of the F-W model (nucleation) describing amyloid-β production in the axon	s^{-1}	7.301×10^{-11}	See the discussion leading to Eq. (S54)
$k^*_{2,ax}\frac{C^*_{s,i}A^*_{ax}}{V^*_s}$	Rescaled rate constant for the second pseudoelementary step of the F-W model (autocatalytic growth) describing amyloid-β production in the axon	s^{-1}	2.627×10^{-11}	See the discussion leading to Eq. (S54)
$k^*_{1,s}$	Rate constant for the first pseudoelementary step of the F-W model (nucleation) describing amyloid-β	s^{-1}	7.301×10^{-11}	See the discussion leading to Eq. (S53)

	production in the soma			
$k_{2,s}^*$	Rate constant for the second pseudoelementary step of the F-W model (autocatalytic growth) describing amyloid-β production in the soma	s^{-1}	2.627×10^{-11}	See the discussion leading to Eq. (S53)
L^*	Length of the axon	μm	600	[1]
$\dot{q}_{APP}^*$	Rate of APP synthesis in the soma per neuron	s^{-1}	115.7 [b]	[2]
$T_{1/2,APP}^*$	Half-life of APP in the soma	s	7.92×10^{3} [c]	[3]
$T_{1/2,A\beta}^*$	Half-life of amyloid-β	s	3.24×10^{4} [d]	[4,5]
v_+^*	Anterograde velocity of APP-transporting vesicles propelled by kinesin motors	μm/s	1.74	[6]
v_-^*	Retrograde velocity of APP-transporting vesicles propelled by dynein motors	μm/s	1.51	[6]
α_+^*	Kinetic constant describing the rate of transition $c_0^* \to c_+^*$	s^{-1}	1 [e]	[7]
α_-^*	Kinetic constant describing the rate of transition $c_0^* \to c_-^*$	s^{-1}	1 [e]	[7]
$\alpha_+'^*$	Kinetic constant describing the rate of transition $c_+^* \to c_0^*$	s^{-1}	0.4609 [e]	[7]
$\alpha_-'^*$	Kinetic constant describing the rate of transition $c_-^* \to c_0^*$	s^{-1}	1 [e]	[7]
σ	Portion of APP vesicles entering the synapse that return to the axon by retrograde transport		0.4609	See the discussion leading to Eq. (S8) and immediately following this equation

	(the rest are destroyed in the synapse)			

[a] Values of h^*_{APP} and $C^*_{s,i}$ were obtained by solving Eqs. (13) and (14).

[b] Approximately 1.7×10^6 molecules of Aβ40 are secreted from an axon per 24 hours [2]. Since approximately 40% of Aβ are secreted from the axon and 60% are secreted from the soma [2], a total of 4.25×10^6 molecules of Aβ40 are secreted from a neuron per 24 hours. There are other APP fragments, such as Aβ42, that are secreted from a neuron. Most of the APP synthesized in the soma is released from the neuron [3]. We assumed that a total of 10^7 APP molecules per 24 hours are produced in a neuron. This gives the rate of APP production per single neuron at approximately 115.7 molecules per second.

[c] Ref. [3] noted that in addition to the main pool of APP, characterized by a half-life of 2.2 h, there is also a smaller surface pool of APP that turns over very slowly.

[d] Ref. [5] reported that the half-life of Aβ can change 2.5-fold with the age, from 3.8 h (1.368×10^4 s) at the age of 30 to 9.4 h (3.384×10^4 s) at the age of 80.

[e] To the best of our knowledge, there is no published experimental data that would allow us to estimate values of kinetic constants for APP transport. Therefore, we relied on ref. [7] and assumed that kinetic constants are of order 1 s^{-1}. We used a value of 1 s^{-1} for α^*_-, α^*_+, and α'^*_- and, based on Eq. (S7), we set $\alpha'^*_+ = 0.4\frac{v^*_+}{v^*_-} = 0.4609$ s^{-1}.

Table S4. Dependent variables in the model of tau transport.

Symbol	Definition	Units
$j^*_{tot,tau}$	Total flux of tau monomers	s^{-1}
n^*_a	Linear number density of on-track tau monomers moving along MTs anterogradely, propelled by molecular motors, in the axon	μm^{-1}
n^*_r	Linear number density of on-track tau monomers moving along MTs retrogradely, propelled by molecular motors, in the axon	μm^{-1}
n^*_{a0}	Linear number density of pausing on-track tau monomers that are still associated with molecular motors and can resume their	μm^{-1}

	anterograde motion, in the axon	
n^*_{r0}	Linear number density of pausing on-track tau monomers that are still associated with molecular motors and can resume their retrograde motion, in the axon	μm^{-1}
n^*_{free}	Linear number density of free (off-track) tau monomers in the cytosol, in the axon	μm^{-1}
n^*_{st}	Linear number density of stationary tau monomers bound to MTs, no association with motors, in the axon	μm^{-1}
n^*_{dif}	Linear number density of tau monomers diffusing along MTs, no association with motors, in the axon	μm^{-1}
$n^*_{mis,ax}$	Linear number density of misfolded tau polymers, no mobility, in the axon	μm^{-1}
N^*_s	Number of tau monomers in the soma	
$N^*_{mis,s}$	Number of misfolded tau polymers in the soma	
$N^*_{mis,tot}$	Total number of tau polymers in the axon and in the soma	

Table S5. Parameters characterizing transport of tau protein and their estimated values. In ref. [8] values of 18 model parameters were determined by finding values that give the best fit between model predictions and experimental results. We denoted values obtained in ref. [8] by LSR (Least Square Regression).

Symbol	Definition	Units	Estimated value	Reference or estimation method
A	Coefficient in Eq. (34)		5.079×10^{-2}	LSR
A_{ax}	Cross-sectional area of the initial segment of the axon	μm^2	0.7854 [a]	[9]
D^*_{free}	Diffusivity of tau protein in the cytosolic state	$\mu m^2/s$	3	[10]
D^*_{mt}	Diffusivity of tau protein along MTs	$\mu m^2/s$	0.153	[11]
h^*_{tau}	Mass transfer coefficient characterizing	s^{-1}	3.518×10^{-7} [b]	See Eqs. (36) and (39)

	transport of tau protein from the soma to the axon			
$j_{tot,tau,x=0}$ [c]	Dimensionless total flux of tau into the axon		3.753×10^{-3}	LSR
$n_{free,x=0}$ [d]	Dimensionless concentration of free (cytosolic) tau at the axon hillock		1.616×10^{-6}	LSR
$n_{dif,x=0}$ [e]	Dimensionless concentration of MT-bound tau protein capable of diffusing along MTs at the axon hillock		7.849×10^{-1}	LSR
$N^*_{s,i}$	Initial number of tau molecules (monomers) in the soma		1.262×10^{7} [f]	See Eq. (S1)
$\dot{q}^*_{tau}$	Rate of tau synthesis in the soma per neuron	s^{-1}	44.94 [b]	See Eqs. (36) and (39)
$T^*_{1/2,free\,tau}$	Half-life of free monomeric tau protein	s	2.16×10^{5} [g]	[12]
$T^*_{1/2,mis\,tau}$	Half-life of misfolded (aggregated) tau protein	s	4.32×10^{5} [h]	See footnote "h" after Table S5
v^*_a, v^*_r	Velocities of rapid motions of tau on MTs propelled by kinesin and dynein motors, respectively	μm/s	0.5, 0.5 [i]	[10]
V^*_s	Volume of the neuron soma	μm^3	4.189×10^{3} [j]	[13]
$\beta^*_{ax}\frac{C^*_{s,i}A^*_{ax}}{V^*_s}$	Coefficient in Eq. (41) simulating the dependence of $\lambda^*_{2,ax}$ on the concentration of amyloid-β in the axon		$0\text{-}10^5$	Investigated range
$\beta_s C^*_{s,i}$	Coefficient in Eq. (42) simulating the		$0\text{-}10^5$	Investigated range

	dependence of $\lambda_{2,s}^{*}$ on the concentration of amyloid-β in the axon			
γ_{10}^{*}	Kinetic constant describing the rate of transitions $n_a^{*} \to n_{a0}^{*}$ and $n_r^{*} \to n_{r0}^{*}$	s^{-1}	1.710×10^{-1} k	LSR
γ_{01}^{*}	Kinetic constant describing the rate of transitions $n_{a0}^{*} \to n_a^{*}$ and $n_{r0}^{*} \to n_r^{*}$	s^{-1}	5.403×10^{-3} k	LSR
γ_{ar}^{*}	Kinetic constant describing the rate of transition $n_{a0}^{*} \to n_{r0}^{*}$	s^{-1}	7.904×10^{-7}	LSR
γ_{ra}^{*}	Kinetic constant describing the rate of transition $n_{r0}^{*} \to n_{a0}^{*}$	s^{-1}	5.988×10^{-5}	LSR
$\gamma_{on,a}^{*}$	Kinetic constant describing the rate of transition $n_{free}^{*} \to n_{a0}^{*}$	s^{-1}	1.072×10^{-2}	LSR
$\gamma_{on,r}^{*}$	Kinetic constant describing the rate of transition $n_{free}^{*} \to n_{r0}^{*}$	s^{-1}	9.985×10^{-6}	LSR
$\gamma_{off,a}^{*}$	Kinetic constant describing the rate of transition $n_{a0}^{*} \to n_{free}^{*}$	s^{-1}	7.996×10^{-7}	LSR
$\gamma_{off,r}^{*}$	Kinetic constant describing the rate of transition $n_{r0}^{*} \to n_{free}^{*}$	s^{-1}	2.833×10^{-9}	LSR
$\gamma_{free \to st}^{*}$	Kinetic constant describing the rate of transition $n_{free}^{*} \to n_{st}^{*}$	s^{-1}	9.978×10^{-6}	LSR
$\gamma_{st \to free}^{*}$	Kinetic constant describing the rate of transition $n_{st}^{*} \to n_{free}^{*}$	s^{-1}	1.651×10^{-5}	LSR
$\gamma_{free \to dif}^{*}$	Kinetic constant describing the rate of transition $n_{free}^{*} \to n_{dif}^{*}$	s^{-1}	4.395×10^{-6}	LSR

$\gamma^*_{dif\to free}$	Kinetic constant describing the rate of transition $n^*_{dif} \to n^*_{free}$	s^{-1}	2.167×10^{-3}	LSR
$\gamma^*_{dif\to st}$	Kinetic constant describing the rate of transition $n^*_{dif} \to n^*_{st}$	s^{-1}	7.924×10^{-7}	LSR
$\gamma^*_{st\to dif}$	Kinetic constant describing the rate of transition $n^*_{st} \to n^*_{dif}$	s^{-1}	8.586×10^{-6}	LSR
$\lambda^*_{1,ax}$	Rate constant for the first pseudoelementary step of the F-W model (nucleation) describing misfolding of free tau in the axon	s^{-1}	3.558×10^{-7}	See the discussion leading to Eq. (S59)
$\lambda^*_{2,ax0}n^*_{tot,ax,x=0}$	Rescaled rate constant for the second pseudoelementary step of the F-W model (autocatalytic growth) describing misfolding of free tau in the axon at $c^*_{A\beta,ax}=0$	s^{-1}	4.021×10^{-14}	See the discussion leading to Eq. (S59)
$\lambda^*_{1,s}$	Rate constant for the first pseudoelementary step of the F-W model (nucleation) describing misfolding of free tau in the soma	s^{-1}	3.558×10^{-7}	See the discussion leading to Eq. (S58)
$\lambda^*_{2,s0}$	Rate constant for the second pseudoelementary step of the F-W model (autocatalytic growth) describing misfolding of free tau in the soma at $C^*_{A\beta,s}=0$	s^{-1}	4.021×10^{-14}	See the discussion leading to Eq. (S58)

[a] We considered a representative situation with a diameter of 1 μm for the initial segment of the axon.

[b] Values of h^*_{tau} and $\dot{q}^*_{tau}$ were obtained by solving Eqs. (36) and (39).

[c] $j_{tot,tau,x=0} = \dfrac{j^*_{tot,tau,x=0}}{n^*_{tot,ax,x=0} v^*_a}$.

[d] $n_{free,x=0} = \dfrac{n^*_{free,x=0}}{n^*_{tot,ax,x=0}}$.

[e] $n_{dif,x=0} = \dfrac{n^*_{dif,x=0}}{n^*_{tot,ax,x=0}}$.

[f] The average tau concentration in a cell, C_μ, is 5 μM [14,15]. Following ref. [16], the initial number of tau molecules in the soma is estimated as:

$$N^*_{s,i} = C_\mu f_\mu V^*_s N_A = \left(5\times10^{-21}\,\text{mol}\,\mu\text{m}^{-3}\right) \times\left(4.19\times10^{3}\,\mu\text{m}^{3}\right)\times\left(6.022\times10^{23}\,\text{mol}^{-1}\right) = 1.262\times10^{7}, \quad \text{(S1)}$$

where N_A is the Avogadro's constant (6.022×10^{23} mol^{-1}), f_μ is the conversion factor ($10^{-21}\dfrac{\text{mol}}{\mu\text{M}\,\mu\text{m}^3}$), and V^*_s is the volume of the soma (4.19×10^{3} μm^3).

[g] Since tau is transported mainly by slow axonal transport mechanism in long axons, on average it moves anterogradely and, therefore, unlike APP, it cannot generally return to the soma for degradation. For this reason, tau's concentration must depend on its half-life in the axon and in the synapse; these can be different values [17].

[h] Misfolded tau in the F-W model represents many different fibril sizes, which may have different half-lives. According to ref. [18], tau aggregates may disrupt proteasome function resulting in a longer half-life of tau aggregates. Due to a lack of published experimental data, as a first approximation, we assumed that $T^*_{1/2,mis}$ is twice the half-life of free monomeric tau.

[i] Parameters v^*_a and v^*_+ characterize the anterograde velocities of tau protein and APP, respectively, due the action of kinesin motors. Because the average size of the cargo, average number of motors transporting the cargo, and other parameters characterizing tau and APP transport are different, v^*_a and v^*_+ take on different values. The same applies to v^*_r and v^*_-.

[j] We considered a representative neuron with a soma diameter of 20 μm.

[k] Recent data suggest that the rates of association and dissociation of tau to/from MTs may be faster than it was previously believed. The dwell time of tau may be as short as 40 ms [15,19], approximately 100-fold shorter than it was reported in ref. [10]. More research is needed to improve estimated values of the kinetic constants that characterize these processes.

Table S6. Dimensionless independent variables in the models of APP and tau transport.

Symbol	Definition
x^*	$\frac{x^* \gamma_{10}^*}{v_a^*}$
t^*	$t^* \gamma_{10}^*$

Table S7. Dimensionless dependent variables in the model of APP transport.

Symbol	Definition
c_+	$\frac{c_+^* V_s^*}{C_{s,i}^* A_{ax}^*}$
c_-	$\frac{c_-^* V_s^*}{C_{s,i}^* A_{ax}^*}$
c_0	$\frac{c_0^* V_s^*}{C_{s,i}^* A_{ax}^*}$
$c_{A\beta,ax}$	$\frac{c_{A\beta,ax}^* V_s^*}{C_{s,i}^* A_{ax}^*}$
C_s	$\frac{C_s^*}{C_{s,i}^*}$
$C_{A\beta,s}$	$\frac{C_{A\beta,s}^*}{C_{s,i}^*}$
$C_{A\beta,tot}$	$\frac{C_{A\beta,tot}^*}{C_{s,i}^*}$
j_{APP}	$\frac{j_{APP}^* V_s^*}{C_{s,i}^* A_{ax}^* v_+^*}$

Table S8. Dimensionless dependent variables in the model of tau transport.

Symbol	Definition
$j_{tot,tau}$	$\frac{j^*_{tot,tau}}{n^*_{tot,ax,x=0} v^*_a}$
n_a	$\frac{n^*_a}{n^*_{tot,ax,x=0}}$
n_r	$\frac{n^*_r}{n^*_{tot,ax,x=0}}$
n_{a0}	$\frac{n^*_{a0}}{n^*_{tot,ax,x=0}}$
n_{r0}	$\frac{n^*_{r0}}{n^*_{tot,ax,x=0}}$
n_{free}	$\frac{n^*_{free}}{n^*_{tot,ax,x=0}}$
n_{st}	$\frac{n^*_{st}}{n^*_{tot,ax,x=0}}$
n_{dif}	$\frac{n^*_{dif}}{n^*_{tot,ax,x=0}}$
$n_{mis,ax}$	$\frac{n^*_{mis,ax}}{n^*_{tot,ax,x=0}}$
N_s	$\frac{N^*_s}{N^*_{s,i}}$
$N_{mis,s}$	$\frac{N^*_{mis,s}}{N^*_{s,i}}$
$N_{mis,tot}$	$\frac{N^*_{mis,tot}}{N^*_{s,i}}$

S2. Solution with constant APP concentrations along the axon for $k^*_{1,ax} = k^*_{2,ax} = 0$

The fluxes of anterogradely and retrogradely transported APP can be found utilizing the following equations, respectively:

$$j^*_{+,APP} = v^*_+ c^*_+ , \tag{S2}$$

$$j^*_{-,APP} = v^*_- c^*_- . \tag{S3}$$

We assumed that v^*_+ and v^*_- (velocities of kinesin and dynein motors, respectively) are constant. Fig. 5a of ref. [6] suggests that approximately 50% of the APP-containing vesicles move anterogradely, 20% move retrogradely, and 30% are stationary. According to Eqs. (S2) and (S3), if $j^*_{+,APP}$ and $j^*_{-,APP}$ are constant, then the concentrations of anterogradely and retrogradely running APP, c^*_+ and c^*_-, must be constant as well. We therefore looked for a solution of Eqs. (1)-(3) with constant concentrations. For the case of $k^*_{1,ax} = k^*_{2,ax} = 0$, which corresponds to a healthy axon, we found the following solution [20]:

$$c^*_- = \frac{\alpha^*_- \alpha'^*_+}{\alpha^*_+ \alpha'^*_-} c^*_+ , \tag{S4}$$

$$c^*_0 = \frac{\alpha'^*_+}{\alpha^*_+} c^*_+ . \tag{S5}$$

Taking the ratio of Eqs. (S3) and (S2), and the ratio of anterogradely and retrogradely transported APP [6], we found that

$$\frac{c^*_-}{c^*_+} = 0.4 \frac{v^*_+}{v^*_-} . \tag{S6}$$

We then compared Eqs. (S4) and (S6), and concluded that the APP concentrations are constant along the axon length if the following relation between the kinetic constants is satisfied:

$$\frac{\alpha^*_- \alpha'^*_+}{\alpha^*_+ \alpha'^*_-} = 0.4 \frac{v^*_+}{v^*_-} . \tag{S7}$$

Using Eqs. (S4) and (S7) we concluded that

$$\sigma = \frac{\alpha^*_- \alpha'^*_+}{\alpha'^*_- \alpha^*_+} = 0.4 \frac{v^*_+}{v^*_-} . \tag{S8}$$

We followed ref. [7] and assumed that the kinetic constants characterizing APP transport between various kinetic states are of order 1 s^{-1}. We used a value of 1 s^{-1} for α_-^*, α_+^*, and $\alpha_-'^*$. Using Eq. (S7) we then obtained that $\alpha_+'^* = 0.4\dfrac{v_+^*}{v_-^*} = 0.4609\ \mathrm{s}^{-1}$. From Eq. (S8) we also found that $\sigma = 0.4609$.

Using the values for v_+^*, v_-^*, α_+^*, α_-^*, $\alpha_+'^*$, and $\alpha_-'^*$ reported in Table S3 as well as Eqs. (S4), (S5), and (10), we obtained that

$$c_+^* = \left(0.9578\,\mathrm{s\,\mu m^{-1}}\right) j_{tot,APP}^*, \tag{S9}$$

$$c_-^* = \left(0.4415\,\mathrm{s\,\mu m^{-1}}\right) j_{tot,APP}^*, \tag{S10}$$

$$c_0^* = \left(0.4415\,\mathrm{s\,\mu m^{-1}}\right) j_{tot,APP}^*. \tag{S11}$$

S3. Equations for APP transport with dimensionless concentrations

Dimensionless APP concentrations were introduced by referring the corresponding dimensional APP concentrations to the number of APP molecules in the soma and multiplying the result by V_s^* / A_{ax}^*, for example:

$$c_+ = \frac{c_+^* V_s^*}{C_{s,i}^* A_{ax}^*}. \tag{S12}$$

The conservation equation for anterogradely transported APP (dimensionless concentration c_+) is

$$-v_+^* \frac{\partial c_+}{\partial x^*} + \alpha_+^* c_0 - \alpha_+'^* c_+ = 0. \tag{S13}$$

The conservation equation for retrogradely transported APP (dimensionless concentration c_-) is

$$v_-^* \frac{\partial c_-}{\partial x^*} + \alpha_-^* c_0 - \alpha_-'^* c_- = 0. \tag{S14}$$

The conservation equation for APP molecules contained in the presynaptic vesicles that are detached from MTs (dimensionless concentration c_0) is

$$-\alpha_+^* c_0 - \alpha_-^* c_0 + \alpha_+'^* c_+ + \alpha_-'^* c_- - k_{1,ax}^* c_0 - \left(k_{2,ax}^* \frac{C_{s,i}^* A_{ax}^*}{V_s^*}\right) c_0 c_{A\beta,ax} = 0. \tag{S15}$$

The conservation equation for extracellular Aβ polymers originating from APP processing at the axon membrane (dimensionless concentration $c_{A\beta,ax}$) is

$$\frac{\partial c_{A\beta,ax}}{\partial t^*} = k^*_{1,ax} c_0 + \left(k^*_{2,ax} \frac{C^*_{s,i} A^*_{ax}}{V^*_s} \right) c_0 c_{A\beta,ax} - \frac{c_{A\beta,ax} \ln(2)}{T^*_{1/2,A\beta}}. \tag{S16}$$

The rescaled number of Aβ polymers originating from APP processing at the axon membrane is defined as:

$$C_{A\beta,ax} = \frac{C^*_{A\beta,ax}}{C^*_{s.i}} = \frac{A^*_{ax}}{V^*_s} \int_0^{L^*} c_{A\beta,ax} dx^*. \tag{S17}$$

The conservation equation for APP molecules synthesized in the soma (rescaled number C_s) is

$$\frac{dC_s}{dt^*} = \frac{\dot{q}^*_{APP}}{C^*_{s,i}} - k^*_{1,s} C_s - \left(k^*_{2,s} C^*_{s,i} \right) C_s C_{A\beta,s} - \frac{C_s \ln(2)}{T^*_{1/2,APP}} - h^*_{APP} C_s, \tag{S18}$$

where

$$C_s = \frac{C^*_s}{C^*_{s,i}}. \tag{S19}$$

The conservation equation for extracellular Aβ polymers originating from APP processing at the soma membrane (rescaled number $C_{A\beta,s}$) is

$$\frac{dC_{A\beta,s}}{dt^*} = k^*_{1,s} C_s + \left(k^*_{2,s} C^*_{s,i} \right) C_s C_{A\beta,s} - \frac{C_{A\beta,s} \ln(2)}{T^*_{1/2,A\beta}}. \tag{S20}$$

Eqs. (S13)-(S15) are solved subject to the following boundary conditions:

$$\frac{j^*_{tot,APP}(0) V^*_s}{C^*_{s,i} A^*_{ax}} = v^*_+ c_+(0) - v^*_- c_-(0) = \frac{h^*_{APP} V^*_s}{A^*_{ax}} C_s, \tag{S21}$$

$$c_-\left(L^*\right) = \sigma c_+\left(L^*\right). \tag{S22}$$

The initial conditions for Eqs. (S16), (S18), and (S20) are

$$\text{At } t^* = 0: \qquad c_{A\beta,ax} = 0, \qquad C_{A\beta,s} = 0, \qquad C_s = 1. \tag{S23}$$

S4. Equations for tau transport with dimensionless concentrations

Dimensionless tau concentrations were introduced by referring the corresponding dimensional tau concentrations to the total concentration of tau protein at the axon hillock, for example:

$$n_a = \frac{n_a^*}{n_{tot,ax,x=0}^*}. \tag{S24}$$

The total concentration of tau monomers at the axon hillock, $n_{tot,ax,x=0}^*$, can be estimated as follows. The volume of the axon is $A_{ax}^* L^*$, the number of tau monomers in the axon can be estimated as $\frac{N_s^*}{V_s^*} A_{ax}^* L^*$, therefore the concentration of tau monomers in the axon is $\frac{N_s^*}{V_s^*} A_{ax}^* L^* \frac{1}{L^*}$.

The conservation equations for anterogradely and retrogradely actively transported tau proteins (dimensionless concentrations n_a and n_r, respectively) are

$$-v_a^* \frac{\partial n_a}{\partial x^*} - \gamma_{10}^* n_a + \gamma_{01}^* n_{a0} = 0, \tag{S25}$$

$$v_r^* \frac{\partial n_r}{\partial x^*} - \gamma_{10}^* n_r + \gamma_{01}^* n_{r0} = 0. \tag{S26}$$

The conservation equations for pausing tau proteins, which are ready to resume their motion in the anterograde and retrograde directions (dimensionless concentrations n_{a0} and n_{r0}, respectively), are

$$-\left(\gamma_{01}^* + \gamma_{ar}^* + \gamma_{off,a}^*\right) n_{a0} + \gamma_{10}^* n_a + \gamma_{ra}^* n_{r0} + \gamma_{on,a}^* n_{free} = 0, \tag{S27}$$

$$-\left(\gamma_{01}^* + \gamma_{ra}^* + \gamma_{off,r}^*\right) n_{r0} + \gamma_{10}^* n_r + \gamma_{ar}^* n_{a0} + \gamma_{on,r}^* n_{free} = 0. \tag{S28}$$

The conservation equation for free (cytosolic) tau (dimensionless concentration n_{free}) is

$$D_{free}^* \frac{\partial^2 n_{free}}{\partial x^{*2}} + \gamma_{off,a}^* n_{a0} + \gamma_{off,r}^* n_{r0} - \left(\gamma_{on,a}^* + \gamma_{on,r}^* + \gamma_{free\to st}^* + \gamma_{free\to dif}^*\right) n_{free} + \gamma_{st\to free}^* n_{st} + \gamma_{dif\to free}^* n_{dif}$$

$$-\lambda_{1,ax}^* n_{free} - \left(\lambda_{2,ax}^* n_{tot,x=0}^*\right) n_{free} n_{mis,ax} - \frac{n_{free} \ln(2)}{T_{1/2,\,free\,tau}^*} = 0. \tag{S29}$$

The conservation equation for misfolded tau (dimensionless concentration $n_{mis,ax}$) is

$$\frac{\partial n_{mis,ax}}{\partial t^*} = \lambda^*_{1,ax} n_{free} + \left(\lambda^*_{2,ax} n^*_{tot,x=0}\right) n_{free} n_{mis,ax} - \frac{n_{mis,ax} \ln(2)}{T^*_{1/2,mis}}. \quad \text{(S30)}$$

The conservation equation for tau that can diffuse along the MTs (dimensionless concentration n_{dif}) is

$$D^*_{mt} \frac{\partial^2 n_{dif}}{\partial x^{*2}} - \left(\gamma^*_{dif\to free} + \gamma^*_{dif\to st}\right) n_{dif} + \gamma^*_{free\to dif} n_{free} + \gamma^*_{st\to dif} n_{st} = 0. \quad \text{(S31)}$$

The conservation equation for tau that is stationary on MTs (dimensionless concentration n_{st}) is

$$-\left(\gamma^*_{st\to free} + \gamma^*_{st\to dif}\right) n_{st} + \gamma^*_{free\to st} n_{free} + \gamma^*_{dif\to st} n_{dif} = 0. \quad \text{(S32)}$$

The total dimensionless concentration of tau is defined as:

$$n_{tot} = n_a + n_r + n_{a0} + n_{r0} + n_{free} + n_{st} + n_{dif} + n_{mis,ax}. \quad \text{(S33)}$$

The percentage of MT-bound tau can be found through the dimensionless concentrations as:

$$\%\text{bound} = \frac{n_a + n_r + n_{a0} + n_{r0} + n_{st} + n_{dif}}{n_{tot,ax}}(100\%). \quad \text{(S34)}$$

The dimensionless flux of tau protein is found as:

$$j_{tot,tau} = \frac{j^*_{tot,tau}}{n^*_{tot,ax,x=0} v^*_a} = -\frac{D^*_{free}}{v^*_a}\frac{\partial n_{free}}{\partial x^*} - \frac{D^*_{mt}}{v^*_a}\frac{\partial n_{dif}}{\partial x^*} + n_a - \frac{v^*_r}{v^*_a} n_r. \quad \text{(S35)}$$

By using $j_{tot,tau}$ and $n_{tot,ax}$, the average tau velocity is found as:

$$v^*_{av} = \frac{j_{tot,tau}}{n_{tot,ax}} v^*_a. \quad \text{(S36)}$$

The rescaled number of misfolded tau polymers in the axon is defined as:

$$N_{mis,ax} = \frac{N^*_{mis,ax}}{N^*_{s,i}} = \frac{n^*_{tot,ax,x=0}}{N^*_{s,i}} \int_0^{L^*} n_{mis,ax} dx^*. \quad \text{(S37)}$$

The conservation equation for tau monomers in the soma (rescaled number N_s) is

$$\frac{dN_s}{dt^*} = \frac{\dot{q}^*_{tau}}{N^*_{s,i}} - \lambda^*_{1,s} N_s - \left(\lambda^*_{2,s} N^*_{s,i}\right) N_s N_{mis,s} - \frac{N_s \ln(2)}{T^*_{1/2,\,free\,tau}} - h^*_{tau} N_s, \quad \text{(S38)}$$

where

$$N_s = \frac{N_s^*}{N_{s,i}^*}. \tag{S39}$$

The conservation equation for tau polymers in the soma (rescaled number $N_{mis,s}^*$) is

$$\frac{dN_{mis,s}}{dt^*} = \lambda_{1,s}^* N_s + \left(\lambda_{2,s}^* N_{s,i}^*\right) N_s N_{mis,s} - \frac{N_{mis,s}\ln(2)}{T_{1/2,mis}^*}. \tag{S40}$$

The rescaled number of misfolded tau polymers in the whole neuron (in the axon and in the soma) is

$$N_{mis,tot} = N_{mis,ax} + N_{mis,s}. \tag{S41}$$

The dimensionless boundary conditions at the axon hillock are

$$\text{At } x = 0: \qquad n_{free} = n_{free,x=0}, \quad j_{tot,tau} = j_{tot,tau,x=0}, \qquad n_{dif} = n_{dif,x=0}, \tag{S42a,b,c}$$

where

$$x = \frac{x^*}{v_a^* T_{1/2}^*}. \tag{S43}$$

The dimensionless tau flux from the soma into the axon is calculated as:

$$j_{tot,tau,x=0} = \frac{j_{tot,tau}^*(0)}{n_{tot,ax,x=0}^* v_a^*} = -\frac{D_{free}^*}{v_a^*}\frac{\partial n_{free}}{\partial x^*}(0) - \frac{D_{mt}^*}{v_a^*}\frac{\partial n_{dif}}{\partial x^*}(0) + n_a(0) - \frac{v_r^*}{v_a^*}n_r(0) = \frac{h_{tau}^* N_{s,i}^*}{n_{tot,ax,x=0}^* v_a^*} N_s. \tag{S44}$$

The dimensionless boundary conditions at the axon terminal are

$$\text{At } x = L: \qquad \frac{\partial n_{free}}{\partial x^*} = 0, \qquad j_{tot,tau} = j_{tot,tau,x=L}, \qquad \frac{\partial n_{dif}}{\partial x^*} = 0, \tag{S45a,b,c}$$

where the boundary condition given by Eq. (45b) can be recast, using the dimensionless concentrations, as:

$$-D_{free}^*\frac{\partial n_{free}}{\partial x^*} - D_{mt}^*\frac{\partial n_{dif}}{\partial x^*} + v_a^* n_a - v_r^* n_r = A\left(1 - \exp\left[-\frac{\ln(2)}{T_{1/2}^*}\frac{1}{\gamma_{ar}^*}\right]\right) v_a^* n_a. \tag{S46}$$

The dimensionless initial conditions are

$$\text{At } t = 0: \; n_{mis,ax}(0) = 0, \; N_{mis,s}^*(0) = 0, \; N_s(0) = 1. \tag{S47}$$

S5. Equations modeling the effect of amyloid-β aggregation on tau agglomeration expressed through dimensionless concentrations

Utilizing the dimensionless concentrations, Eqs. (41) and (42) can be recast as follows:

$$\lambda_{2,ax}^{*}=\tilde{\lambda}_{2,ax0}^{*}\left(1+\beta_{ax}^{*}\frac{C_{s,i}^{*}A_{ax}^{*}}{V_{s}^{*}}c_{A\beta,ax}\right), \tag{S48}$$

$$\lambda_{2,s}^{*}=\tilde{\lambda}_{2,s0}^{*}\left(1+\beta_{s}C_{s,i}^{*}C_{A\beta,s}\right). \tag{S49}$$

S6. Estimating values of kinetic constants $k_{1,ax}^{*}$, $k_{2,ax}^{*}$, $k_{1,s}^{*}$, and $k_{2,s}^{*}$ describing aggregation of APP fragments into amyloid-β

At steady-state, when the production of APP in the soma is compensated by its loss, Eq. (S18) can be rewritten as:

$$\frac{\dot{q}_{APP}^{*}}{C_{s,i}^{*}}-k_{1,s}^{*}C_{s,t\to\infty}-\left(k_{2,s}^{*}C_{s,i}^{*}\right)C_{s,t\to\infty}C_{A\beta,s,t\to\infty}-\frac{C_{s,t\to\infty}\ln(2)}{T_{1/2,APP}^{*}}-h_{APP}^{*}C_{s,t\to\infty}=0. \tag{S50}$$

At the initial moment, $t^{*}=0$, Eq. (S18) can be recast as:

$$\left.\frac{dC_{s}}{dt^{*}}\right|_{t=0}=\frac{\dot{q}_{APP}^{*}}{C_{s,i}^{*}}-k_{1,s}^{*}C_{s,t=0}-\left(k_{2,s}^{*}C_{s,i}^{*}\right)C_{s,t=0}C_{A\beta,s,t=0}-\frac{C_{s,t=0}\ln(2)}{T_{1/2,APP}^{*}}-h_{APP}^{*}C_{s,t=0}. \tag{S51}$$

We assumed that $C_{s,t=0}=1$, $C_{s,t\to\infty}=0.7$, $C_{A\beta,s,t=0}=0$, and $C_{A\beta,s,t\to\infty}=0.3$. We then estimated that $\left.\frac{dC_{s}}{dt^{*}}\right|_{t=0}=\frac{C_{s,t=0}-C_{s,t\to\infty}}{2.5\times365\times24\times3600\,\mathrm{s}}$ and solved Eqs. (S50) and (S51) for $k_{1,s}^{*}$ and $k_{2,s}^{*}$. This resulted in

$$k_{1,s}^{*}=7.301\times10^{-11}\ \mathrm{s}^{-1},\ k_{2,s}^{*}=2.627\times10^{-10}\ \mathrm{s}^{-1}. \tag{S52}$$

Values given by Eq. (S52) are only estimates of the parameters $k_{1,s}^{*}$ and $k_{2,s}^{*}$. In our computations we reduced the value of $k_{2,s}^{*}$ by a factor of 10 to avoid excessively high production of amyloid-β. We thus used:

$$k_{1,s}^{*}=7.301\times10^{-11}\ \mathrm{s}^{-1},\ k_{2,s}^{*}=2.627\times10^{-11}\ \mathrm{s}^{-1}. \tag{S53}$$

We also set $k^*_{1,ax}$ and $k^*_{2,ax}\dfrac{C^*_{s,i}A^*_{ax}}{V^*_s}$ to the same values:

$$k^*_{1,ax} = 7.301\times10^{-11}\ \text{s}^{-1},\ k^*_{2,ax}\frac{C^*_{s,i}A^*_{ax}}{V^*_s} = 2.627\times10^{-11}\ \text{s}^{-1}. \quad \text{(S54)}$$

S7. Estimating values of kinetic constants $\lambda^*_{1,ax}$, $\lambda^*_{2,ax0}$, $\lambda^*_{1,s}$, and $\lambda^*_{2,s0}$ describing aggregation of tau into oligomers and NFTs

At steady-state, when the production of tau monomers in the soma is compensated by their loss, Eq. (S38) can be rewritten as:

$$\frac{dN_s}{dt^*} = \frac{\dot{q}^*_{tau}}{N^*_{s,i}} - \lambda^*_{1,s}N_{s,t\to\infty} - \left(\lambda^*_{2,s0}N^*_{s,i}\right)N_{s,t\to\infty}N_{mis,s,t\to\infty} - \frac{N_{s,t\to\infty}\ln(2)}{T^*_{1/2,\,free\,tau}} - h^*_{tau}N_{s,t\to\infty}. \quad \text{(S55)}$$

At the initial moment, $t^* = 0$, Eq. (S38) can be recast as:

$$\left.\frac{dN_s}{dt^*}\right|_{t=0} = \frac{\dot{q}^*_{tau}}{N^*_{s,i}} - \lambda^*_{1,s}N_{s,t=0} - \left(\lambda^*_{2,s0}N^*_{s,i}\right)N_{s,t=0}N_{mis,s,t=0} - \frac{N_{s,t=0}\ln(2)}{T^*_{1/2,\,free\,tau}} - h^*_{tau}N_{s,t=0}. \quad \text{(S56)}$$

We assumed that $N_{s,t=0} = 1$, $N_{s,t\to\infty} = 0.7$, $N_{mis,s,t=0} = 0$, and $N_{s,t\to\infty} = 0.3$. We then estimated that $\left.\dfrac{dN_s}{dt^*}\right|_{t=0} = \dfrac{N_{s,t=0} - N_{s,t\to\infty}}{2.5\times365\times24\times3600\,\text{s}}$ and solved Eqs. (S55) and (S56) for $\lambda^*_{1,s}$ and $\lambda^*_{2,s0}$. This resulted in

$$\lambda^*_{1,s} = 3.558\times10^{-7}\ \text{s}^{-1},\ \lambda^*_{2,s0} = 4.021\times10^{-13}\ \text{s}^{-1}. \quad \text{(S57)}$$

Values of $\lambda^*_{1,s}$ and $\lambda^*_{2,s0}$ given by Eq. (S57) are only estimates of these parameters. In order to avoid excessively high production of misfolded tau polymers, we reduced a value of $\lambda^*_{2,s0}$ in our computations by a factor of 10. We thus used:

$$\lambda^*_{1,s} = 3.558\times10^{-7}\ \text{s}^{-1},\ \lambda^*_{2,s0} = 4.021\times10^{-14}\ \text{s}^{-1}. \quad \text{(S58)}$$

We also set $\lambda^*_{1,ax}$ and $\lambda^*_{2,ax}n^*_{tot,x=0}$ to the same values:

$$\lambda^*_{1,ax} = 3.558\times10^{-7}\ \text{s}^{-1},\ \lambda^*_{2,ax0} = 4.021\times10^{-14}\ \text{s}^{-1}. \quad \text{(S59)}$$

S8. Evaluation of neurotoxic effects of amyloid-β and tau

Neurotoxicity caused by amyloid-β and tau is a cumulative effect with time [21]. We propose that the percentage of surviving neurons in a certain area of the brain can be evaluated as:

$$S(t)=\left(1-\exp\left(-a_{A\beta}\int_0^t C_{A\beta,tot}dt\right)\right)\left(1-\exp\left(-a_{tau}\int_0^t N_{mis,tot}dt\right)\right)(100\%), \qquad \text{(S60)}$$

where $a_{A\beta}$ and a_{tau} are the kinetic constants characterizing neurotoxicity of amyloid-β and tau, respectively. The values of $a_{A\beta}$ and a_{tau} are expected to be small because neurodegeneration in AD occurs slowly.

One should be cautious when using Eq. (60) because Aβ and tau oligomers are reported to be more toxic than fibrils [21]. In order to distinguish toxic effects of oligomers and fibrils, it is necessary to use a more accurate model than the F-W model, one which would distinguish between polymers of different lengths.

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