Diffusion Model of AMPA Receptor Trafficking and Expression of LTP/LTD

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Introduction

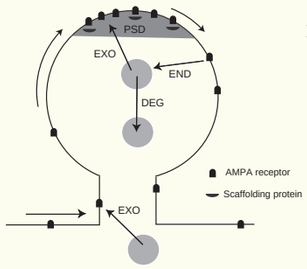
Motivation

- AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors mediate the majority of fast excitatory synaptic transmission in the central nervous system (CNS).
- Experimental evidence suggests that fast AMPA receptor trafficking at the synapses contributes to persistent, activity-dependent changes in synaptic strength, such as long term potentiation (LTP) and depression (LTD).
- Such changes are thought to be necessary subcellular components of learning and memory.
- The precise mechanisms underlying the activity-dependent regulation of AMPA receptor trafficking are currently not known.

Goals of Study

- Develop a mathematical model of AMPA receptor trafficking that includes all trafficking pathways.
- Use the model to examine trafficking under basal conditions and explore the mechanisms underlying activity-dependent trafficking.

AMPA Receptor Trafficking



Postsynaptic Trafficking Pathways[1]

- Synthesis and degradation of receptors in intracellular pools.
- Exo/endocytic exchange of surface receptors with intracellular pools.
- Lateral diffusion of surface receptors in the extrasynaptic membrane (ESM) and postsynaptic density (PSD).
- Binding/unbinding to scaffolding proteins in the PSD.

Two Types of AMPA Receptors at CNS Excitatory Synapses[10]

- Type I: Long C-terminus tail, usually composed of GluR1 and GluR2 subunits. This type is thought to be responsible for LTP.
- Type II: Short C-terminus tail, usually composed of GluR2 and GluR3 subunits. This type is thought to be responsible for constitutive recycling under basal conditions and LTD.

References

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Acknowledgements

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Diffusion Model of AMPA Receptor Trafficking

Type I (GluR1/2) Equations

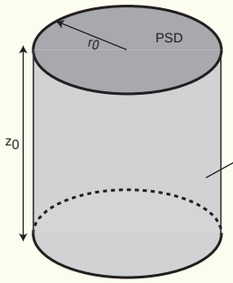
$$\frac{\partial P_I}{\partial t} = D_{rI}\nabla^2 P_I - \alpha_I(L - Q_I - Q_{II})P_I + \beta_I Q_I, \quad 0 \le r < r_0$$
$$\frac{\partial Q_I}{\partial t} = \alpha_I(L - Q_I - Q_{II})P_I - \beta_I Q_I, \quad 0 \le r < r_0$$
$$\frac{\partial R_I}{\partial t} = D_{zI}\nabla^2 R_I - k_I R_I + \kappa_I S_I/A_z, \quad 0 < z < z_0$$
$$\frac{dS_I}{dt} = -\kappa_I S_I + \sigma_I$$

Type II (GluR2/3) Equations

$$\frac{\partial P_{II}}{\partial t} = D_{rII}\nabla^2 P_{II} - \alpha_{II}(L - Q_I - Q_{II})P_{II} + \beta_{II}Q_{II} + \sigma_{II}/A_r, \quad 0 \le r < r_0$$
$$\frac{\partial Q_{II}}{\partial t} = \alpha_{II}(L - Q_I - Q_{II})P_{II} - \beta_{II}Q_{II}, \quad 0 \le r < r_0$$
$$\frac{\partial R_{II}}{\partial t} = D_{zII}\nabla^2 R_{II} - k_{II}R_{II}, \quad 0 < z < z_0$$

Boundary Conditions

$$J_{rI}(r_0) = h_I(P_I(r_0) - R_I(0))$$
$$J_{rII}(r_0) = h_{II}(P_{II}(r_0) - R_{II}(0))$$
$$\Omega_I J_{zI}(z_0) = R_I(z_0) - R_{I0}$$
$$\Omega_{II} J_{zII}(z_0) = R_{II}(z_0) - R_{II0}$$

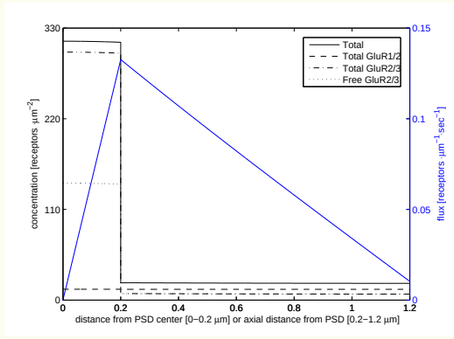


Model geometry of dendritic spine

Definitions
P = concentration of free receptors in the PSD
Q = concentration of bound receptors in the PSD
R = concentration of receptors in the ESM
S = number of receptors in intracellular pool
D_r = diffusivity in the PSD
D_z = diffusivity in the ESM
L = concentration of active binding sites in the PSD
α = rate of binding to active binding sites
β = rate of unbinding from active binding sites
σ = basal rate of exocytosis
κ = dynamic rate of exocytosis per intracellular receptor
k = rate of endocytosis
J_r = flux of free receptors in the PSD
J_z = flux of free receptors in the ESM
h = PSD-ESM junction hopping rate
Ω = diffusive impedance at ESM-dendritic shaft junction
R_0 = background receptor concentration in dendritic shaft

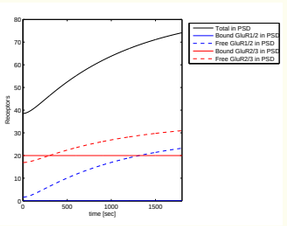
Steady-state Trafficking under Basal Conditions

Steady-state receptor concentration and flux

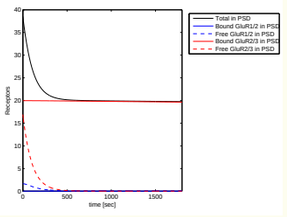


- The majority of receptors in the PSD (ESM) are GluR2/3 (GluR1/2).
- The positive flux represents a PSD-to-ESM flux, and the negligible flux at the ESM-shaft junction means receptors were endocytosed.
- Together, we have constitutive recycling of GluR2/3 receptors.
- These results are consistent with Nusser et al., 1998, and Cottrell et al., 2000.

Blockade of Endocytosis



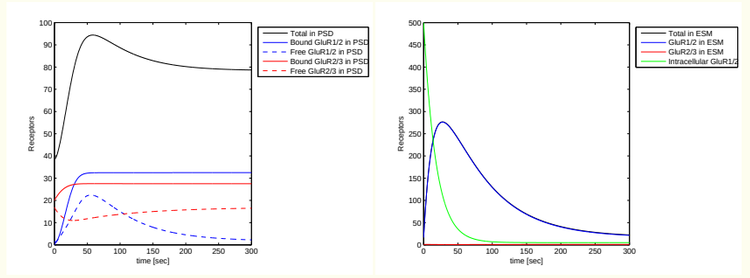
Blockade of Exocytosis



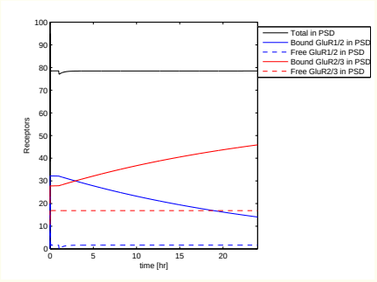
- These time courses are consistent with Luscher et al., 1999.

Trafficking during LTP

To induce LTP, we increase the type I dynamic rate of exocytosis κ_I, hopping rate h_I, and binding rate α_I, and increase the concentration of active binding sites L.



Time course of receptors in PSD and ESM during LTP



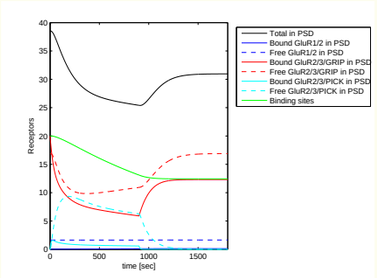
Exchange of GluR1/2 for GluR2/3 after LTP

- The LTP time courses are consistent with Hanse and Gustafsson, 1992, and O' Connor et al., 2005.
- The exchange time courses are consistent with McCormack et al., 2006.

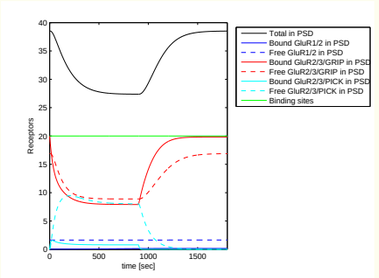
Trafficking during LTD

To induce LTD, we use an extended model to capture the GRIP-to-PICK association change of GluR2/3 receptors, and the loss of active binding sites:

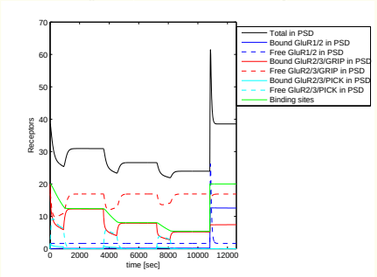
$$\frac{\partial Q_{II}}{\partial t} = \alpha_{II}(L - Q_I - Q_{II} - Q^*_{II})P_{II} - \beta_{II}Q_{II} - \mu Q_{II} + \nu Q^*_{II}, \quad 0 \le r < r_0$$
$$\frac{\partial Q^*_{II}}{\partial t} = -\beta^*_{II}Q^*_{II} + \mu Q_{II} - \nu Q^*_{II}, \quad 0 \le r < r_0$$
$$\frac{\partial L}{\partial t} = -\gamma(L - Q_I - Q_{II} - Q^*_{II}), \quad 0 \le r < r_0$$



Time course of receptors in PSD during low-frequency stimulus, resulting in LTD



Time course of receptors in PSD during medium-frequency stimulus, with no LTD



Saturation of LTD, then LTP

- The LTD time courses are consistent with Dudek and Bear, 1992.
- The saturation time courses are consistent with Dudek and Bear, 1993.