

Comparison of CaMKinase II activation in a dendritic spine computed with deterministic and stochastic models of the NMDA synaptic conductance

Yin Li, William R. Holmes*

Neuroscience Program, Department of Biological Sciences, Irvine Hall 108, Ohio University, Athens, OH 45701-2979, USA

Accepted 13 January 2000

Abstract

In models of long-term potentiation the NMDA conductance is usually computed deterministically. However, the actual number of open NMDA receptor channels at a synapse is small, so a deterministic representation may not be valid. Here NMDA synaptic conductances computed stochastically with MCell were used in a dentate granule cell model that computed calcium influx and subsequent CaMKinase II activation in a dendritic spine following LTP induction conditions. Spine head calcium concentration and levels of CaMKinase II activation were highly variable with different stochastic simulations of NMDA channel openings. This variability in CaMKinase II activity levels due to stochastic NMDA channel openings may play an important role in LTP induction in individual spines. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: CaMKII; LTP; NMDA; Dendritic spine; Hippocampus

1. Introduction

Long-term potentiation (LTP) can be induced in dentate granule cells of the hippocampus with strong, short high-frequency tetanic stimulation. Induction of LTP in the dentate depends on calcium influx through NMDA receptor channels. Recent evidence suggests that calcium influx through NMDA receptor channels may induce LTP by activating calcium/calmodulin-dependent protein kinase II (CaMKinase II).

* Corresponding author. Tel.: +1-740-593-0075; fax: +1-740-593-0300.
E-mail address: holmes@ohiou.edu (W.R. Holmes).

Calcium entering the spine binds to calmodulin, and the calcium–calmodulin complex binds to individual subunits of CaMKinase II and activates them. Models have been developed to gain an understanding of how this process might work [5,2].

Because calcium influx through NMDA receptor channels plays a key role in this process, it is important that the synaptic NMDA conductance be modeled appropriately. Early models represented the NMDA conductance with a double exponential function. More recently, deterministic models of glutamate release, diffusion in the synaptic cleft, and binding to NMDA and non-NMDA receptors have been developed [3], and the NMDA conductance calculated with these models has been used in neuron level models. However, these deterministic synapse level models suggest that only a small number of NMDA receptor channels are open at a given moment. Deterministic representations of the NMDA conductance may not be valid with such small numbers of open channels.

Here we compare model results obtained with deterministic and stochastic representations of the NMDA conductance. Specifically, we explore how the stochastic variability of NMDA receptor channel openings affects calcium influx, spine head calcium concentration and levels of CaMKinase II activation in a dendritic spine following LTP induction stimulation conditions.

2. Methods

Models on three levels were used in this study — neuron level, synapse level, and molecular level. The neuron level model was a fully reconstructed dentate granule cell with voltage-dependent conductances on the soma, axon, and dendrites as described previously [4]. Voltage in the cell was computed following an 8 pulse 400 Hz tetanus applied to 300 medial perforant path synapses. Non-NMDA and NMDA conductances were modeled at activated synapses on dendritic spines.

On the synapse level the non-NMDA and NMDA conductances were computed either deterministically or stochastically with models of glutamate release, diffusion, uptake and binding to receptors. Deterministic conductances were computed as in [3]. Stochastic conductances were computed with MCell [6]. Ten different stochastic NMDA conductance representations were computed using different random seeds. Synaptic conductances used in the neuron level model were deterministic except for the NMDA conductance on one representative spine. The NMDA conductance on this spine was either deterministic or one of the ten stochastic representations. The voltage computed in the neuron level model was used to reduce the NMDA conductance (when the conductance was deterministic) or reduce the number of open NMDA receptor channels (when the conductance was stochastic) taking into account voltage-dependent magnesium block. Computations were done to determine the calcium component of the current through NMDA receptor channels at the representative dendritic spine.

The molecular level model computed calcium concentration and CaMKinase II activation within the dendritic spine as described in [2]. Calcium ions entering the spine either bind to calmodulin, diffuse to neighboring compartments, or are pumped out of the cell. Calmodulin with 0–4 calcium ions bound can bind to a CaMKinase II

subunit. A CaMKinase II subunit is active and is considered “bound” when calmodulin with 4 calcium ions (CaM Ca_4) is bound to it. CaMKinase II subunits can undergo transitions from the “bound” state to “trapped” to “autonomous” and “capped” states as described by Michelson and Schulman [5]. Total CaMKinase II activation was computed as a function of the number of subunits in the bound, trapped, autonomous, and capped states taking into account the different relative activities of these states.

3. Results

The number of open NMDA receptor channels when there was no magnesium block showed considerable variation among the 10 stochastic NMDA conductance simulations. The peak number of open channels varied from 4–9 compared to a peak of less than 4 in the deterministic NMDA conductance simulation (Fig. 1). Whereas the number of open channels varied in integer jumps representing individual channel openings in the stochastic simulations, the number of open channels varied smoothly in the deterministic simulation giving the unrealistic situation of having fractional channel openings. When the 10 stochastic runs were averaged, the result was very similar to the smooth curve computed with the deterministic model. One other notable difference was that late channel openings were occasionally seen in the stochastic simulations after a long period of zero channel openings.

The differences between the use of stochastic and deterministic representations of the NMDA conductance were more apparent when the effect of magnesium block was considered. In the stochastic simulations the number of open, unblocked channels showed the fast flicker observed by Ascher and Nowak [1] and others (Fig. 2). The number of open channels jumped rapidly and often in integer jumps between 0 and 4 indicating that the calcium current through these channels occurred in short bursts. In contrast, the number of open, unblocked channels in the deterministic simulation varied smoothly and was always (the unrealistic value of) less than half of a channel.

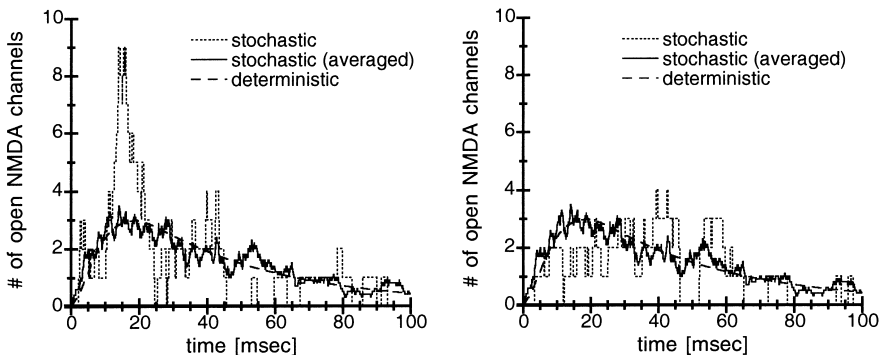


Fig. 1. Two examples of stochastic NMDA channel openings without magnesium block in response to an 8 pulse 400 Hz tetanus. Individual stochastic simulations show considerable variation whereas the average of ten such simulations is similar to the smooth curve computed with the deterministic model.

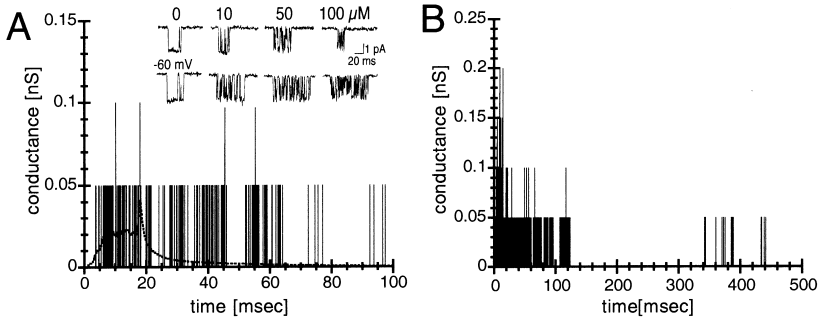


Fig. 2. Stochastic NMDA conductance shows even greater variability with magnesium block included in response to an 8 pulse 400 Hz tetanus. A. Stochastic simulations show the fast flicker between magnesium blocked and unblocked states observed in experiments (inset figure adapted from [1]). The dashed line is the NMDA conductance computed deterministically. B. Sometimes NMDA channel openings (unblocked) were observed long after the termination of the tetanus.

Peak spine head calcium concentration varied from 17 to 45 μM among simulations with the stochastic NMDA conductance compared to 24 μM when the NMDA conductance was represented deterministically. The calcium concentration had numerous large jumps as channels flickered open and closed (Fig. 3). Late openings of NMDA receptor channels, noted above, produced late significant calcium transients in the stochastic simulations. When the calcium concentrations computed with the 10 stochastic NMDA conductance samples were averaged, the result matched the deterministic value very closely except during 20 msec of the decay phase, but this difference could be attributed to having only 10 samples in the computation.

The stochastic variability in spine head calcium concentration caused highly variable levels of “bound” and activated CaMKinase II subunits (Fig. 4). CaMKinase II activation had a short highly activated stage lasting up to 1 s when subunits were primarily in the “bound” state. In this stage total CaMKinase II activation varied from 53 to 90% of the maximum activation among runs with the stochastic NMDA conductance, but peaked at 68% when the NMDA conductance representation was deterministic. A second stage of CaMKinase II activation lasted 1–40 s and was determined largely by the decay of subunits from the “trapped” state. With a single tetanus the peak number of subunits in the trapped state ranged from 30 to 125 in simulations with the stochastic NMDA conductance compared to 50 in the simulation with the deterministic NMDA conductance (results not shown). A third stage of CaMKinase II activation was best seen after the tetanus was repeated 10 times at 4 s intervals. This stage lasted up to 2 h beyond the last tetanus and during this stage CaMKinase II activation ranged from 12 to 30% of maximum when the NMDA conductance was stochastic compared to 20% when the NMDA conductance was deterministic.

4. Discussion

With the number of NMDA channel openings at a synapse being very small, stochastic variations become important for calcium influx into spines during LTP

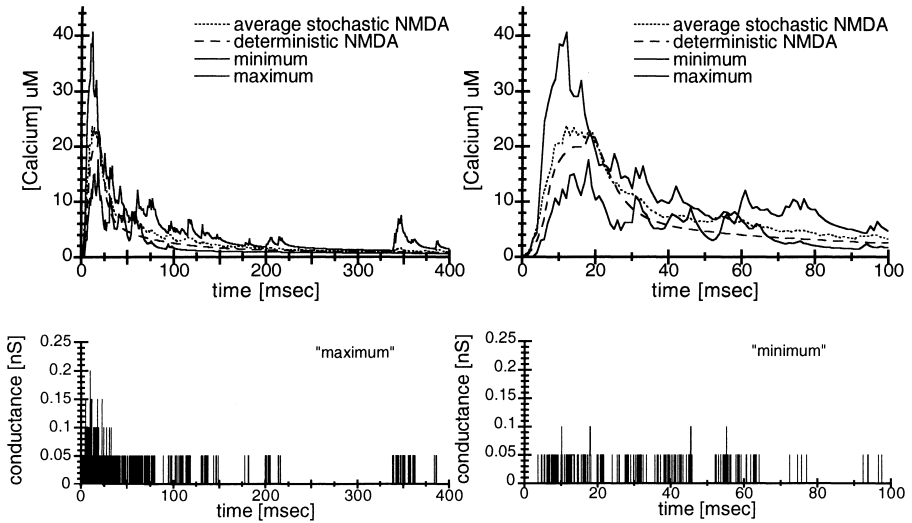


Fig. 3. Spine head calcium concentration varies considerably with different stochastic NMDA conductances, but was similar to the deterministic result on average. The right-top figure is the same as the left-top but on a slower time scale. Bottom figures are the NMDA conductance corresponding to the “maximum” and “minimum” calcium transients in the top figures (the bottom-right figure has a slower time scale). The “maximum” example has the highest CaM Kinase II activation, but not the highest peak calcium concentration.

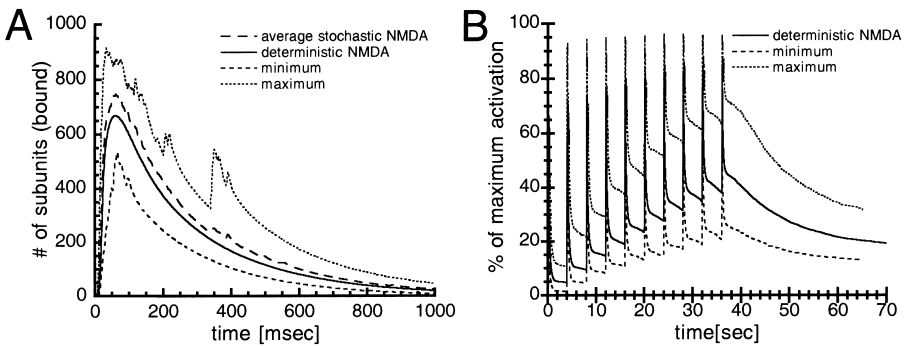


Fig. 4. Differences in spine head calcium concentration translate into different numbers of bound and activated CaMKinase II subunits. A. Bound subunits for stochastic and deterministic NMDA conductances. B. The range of CaMKinase II activation among the stochastic simulations when the 8 pulse 400 Hz tetanus was repeated 10 times at 4 s intervals.

inducing stimulation conditions. The highly variable spine head calcium concentration and subsequent variability in the number of CaMKinase II subunits in the “bound” and “trapped” states found in these simulations could mean that LTP may be induced more reliably in some spines than in others even if the spines are otherwise identical.

In the simulations above, the same stochastic NMDA conductance was used at each tetanus repetition; if different stochastic NMDA conductance representations had been used for each of the 10 tetani, then some of the variability in CaMKinase II activation, at least in the third stage of activation, might have been reduced. In this case, the need to repeat strong, short, high-frequency tetani at regular intervals to induce LTP might also play the role of reducing the variability in the extent of LTP induced at activated synapses.

Acknowledgements

This work was supported by National Institute of Mental Health Grant MH-51081 to WR Holmes. We thank WB Levy and NL Desmond for the anatomical data of the dentate granule cell used in the simulations.

References

- [1] P. Ascher, L. Nowak, The role of divalent cations in the N-methyl-D-aspartate responses of mouse central neurones in culture, *J. Physiol. Lond.* 399 (1988) 247–266.
- [2] W.R. Holmes, Models of calmodulin trapping and CaM Kinase II activation in a dendritic spine, *J. Comput. Neurosci.* 8 (2000) 65–85.
- [3] W.R. Holmes, Modeling the effect of glutamate diffusion and uptake on NMDA and non-NMDA receptor saturation, *Biophys. J.* 69 (1995) 1734–1747.
- [4] W.R. Holmes, W.B. Levy, Quantifying the role of inhibition in associative long-term potentiation in dentate granule cells with computational models, *J. Neurophysiol.* 78 (1997) 103–116.
- [5] S. Michelson, H. Schulman, CaM kinase: A model for its activation and dynamics, *J. Theoret. Biol.* 171 (1994) 281–290.
- [6] J.R. Stiles, T.M. Bartol, E.E. Salpeter, M.M. Salpeter, Monte Carlo simulation of neurotransmitter release using MCell, a general simulator of cellular physiological processes, in: J.M. Bower (Ed.), *Computational Neuroscience: Trends in Research*, Plenum Press, New York, 1998, pp. 274–284.



Yin Li received his B.S. degree in Biological Sciences from the University of Science and Technology of China, China. He has been a graduate student pursuing a Ph.D. degree in neuroscience in the Department of Biological Sciences at Ohio University since 1997. His research interests include computational modeling of hippocampal neurons and synapses. The current work focuses on cooperation of stochastic and deterministic modeling of synaptic and postsynaptic events during LTP induction in dentate granule cells.



Bill Holmes received his Ph.D. from the Department of Biomathematics at UCLA. Currently he is an Associate Professor in the Neuroscience Program in the Department of Biological Sciences at Ohio University. Research interests include the development of mathematical and computational models of individual neurons of the hippocampus that will be appropriate for use in network models to explore hippocampal function. The immediate focus is to develop models of dentate granule cells that describe how computation and synaptic modification occur in these cells.