Effects of short-term synaptic plasticity in a local microcircuit on cell firing.

David Eriksson, Erik Fransén, Yuri Zilberter*, Anders Lansner

Dept. of Numerical Analysis and Computer Science
Royal Institute of Technology
SE-100 44 Stockholm, Sweden

*Dept. of Neuroscience
Karolinska Institutet
SE-171 77 Stockholm, Sweden

Abstract

Effects of short-term synaptic plasticity on cell firing properties in a microcircuit formed by a reciprocally connected pyramidal cell and FSN interneuron in layer 2/3 of neocortex were analyzed in a biophysical model. Induction of synaptic depression by backpropagating dendritic action potentials was replicated, as well as the resulting time dependent depression of IPSP amplitudes. Preliminary results indicate that the effect of the depression becomes significant above 30 Hz input frequency. The magnitude of the effect depends on the time constant of the dendritic calcium regulating the depression. The frequency range depends on the time constant of the IPSP.

Experimental background

Dual whole-cell recordings were made in layer 2/3 of the rat neocortex in synaptically connected pyramidal cells and fast-spiking non-accommodating (FSN) interneurons. In 75% of cell pairs (n=80), the cells formed reciprocal synaptic connections. Trains of backpropagating action potentials (APs) in pyramidal cells induced Ca^{2+} transients in dendrites followed by inhibition of unitary IPSPs (Zilberter 2000). In 16 cell pairs, the mean IPSPs decreased during conditioning to 68±18% of control. The onset time of synaptic depression was within one second and transmission recovered during one minute. Synaptic depression was dependent on a rise in dendritic Ca^{2+} with a threshold at about 40 nM $[Ca^{2+}]_i$, and saturating at about 1 µM $[Ca^{2+}]_i$. Depression was prevented by loading pyramidal cells with exogenous Ca^{2+} buffers, 5 mM BAPTA or EGTA. Paired-pulse depression of IPSPs decreased significantly following the AP bursts suggesting the presynaptic expression of depression. IPSP depression was mimicked by the metabotropic glutamate receptor (mGluR) agonist ACPD and was prevented by a mixture of the mGluR antagonists CPCCOEt and EGLU, indicating that activation of mGluRs underlies this form of synaptic modulation. We concluded that presynaptic mGluRs are activated by a retrograde messenger, presumably glutamate, released from pyramidal cell dendrites following backpropagating APs. Glutamate activates presynaptically located mGluRs receptors that results in inhibition of FSN terminal Ca^{2+} channels via a G-protein dependent pathway leading to a reduction in GABA release.

Modeling methods

Biophysical multicompartmental neuronal simulations were performed using the

NEURON simulation package (Hines et al 1999).

The layer 2/3 neocortical pyramidal cell was modeled according to Bush and Sejnowski (1993) for the passive compartmental representation, and according to Lytton and Sejnowski (1991) for the kinetics of ion channels. Ion channel conductances were tuned to replicate basic electrophysiological characteristics (Zilberter 2000; Mason, Larkman 1990). For the FSN interneuron the same set of parameters were used, except that the Ca-current and the Ca-dependent K-current were omitted yielding a non-adapting cell, and with a change of the conductance of the leakage K-current, yielding a cell with shorter soma membrane time constant and higher input resistance. Short-term synaptic depression at the connections between the FSN and the pyramidal cell were modeled according to Varela et al (1997).

The pyramidal cell and the interneuron were reciprocally connected. When present, the pyramidal to pyramidal connection is very weak, 0.2 mV EPSP amplitude (Zilberter, unpublished observations) and was therefore omitted. FSN to FSN connections appears absent (Zilberter, unpublished observations), and were also omitted.

The fast component of the conditioning induced short-term synaptic depression of the inhibitory synapse was modeled according to Zilberter (2000) and Kaiser et al (2001). The same type of model formalism was used as in Varela et al (1997).

Results

Induction of synaptic depression by backpropagating dendritic action potentials leading to elevated Ca-levels followed by release of a retrograde messenger were replicated, as well as the resulting time dependent depression of IPSP amplitudes. In the microcircuit simulations, the cells were driven by a constant stimulation frequency that was varied between simulations. Preliminary results indicate that at low input frequencies, up to around 30 Hz the effect of the depression is rather small, but increase thereafter. The magnitude of the effect depends on the time constant of the dendritic calcium that regulates the depression. The input frequency at which the influence changes from small to substantial depends on the magnitude of the inhibitory synaptic conductance. It also depends on the time constant of the spike frequency adaptation as well as on the time constant of the cell membrane.

FIGURE 1 Influence of the short-term depression for a range of input frequencies. Both cells receive excitatory input of the same frequency. The resulting firing of the pyramidal cell was compared between a simulation including the short-term plasticity and one without it. The difference within a window of 1 sec, was plotted versus input frequency (Hz). Top: difference of number of spikes with and without plasticity. Bottom: scalar product of inter spike interval distribution vector with and without plasticity.

Discussion

Microcircuit interactions play a crucial role in determining the response of a pyramidal cell to afferent input. We show here how a conditioning induced short-term synaptic depression affects the interplay between a pyramidal cell and an interneuron which are

reciprocally connected, essentially modulating the gain in the negative feed-back from the interneuron to the pyramidal cell.

Due to the relative slow kinetics of the induction of the depression, short lasting inputs will be relatively unaffected by the depression and be subject to the full resting level of inhibitory IPSP amplitudes. Inputs lasting long enough for depression of IPSPs to develop, will however be less attenuated. Excitability and firing frequencies will therefore be higher.

At present we are studying which components of the model are the primary determinants of the effect of the depression on local network spiking activity. The study will continue by repeating the analysis for a random (Poisson) input driving frequency and measure the effects on the inter-spike histogram distribution.

References

Bush P and Sejnowski T. Reduced compartmental models of neocortical pyramidal cells. J. Neurosci. Methods 46: 159-166, 1993.

Hines M, Carnevale N, Moore J and Shepherd G. Using the NEURON simulation environment. Society for Neuroscience meeting satellite symposium, 1999.

Kaiser K, Zilberter Y, Sakmann B. Back-propagating action potentials mediate calcium signalling in dendrites of bitufted interneurons in layer 2/3 of rat somatosensory cortex. J. Physiol. 535.1, 17-31, 2001.

Lytton W and Sejnowski T. Simulations of cortical pyramidal neurons synchronized by inhibitory interneurons.
J. Neurophysiol. 65; 1059-1079, 1991.

Mason A and Larkman A. Correlations between morphology and electrophysiology of pyramidal neurons in slices of rat visual cortex. II Electrophysiology. J. Neurosci. 10: 1415-1428, 1990.

Varela J, Sen K, Gibson J, Fost J, Abbott, L and Nelson S. A Quantitative description of short-term plasticity at excitatory synapses in layer 2/3 of rat primary visual cortex. J. Neurosci. 17: 7926-7940, 1997.

Zilberter Y. Dendritic release of glutamate suppresses synaptic inhibition of pyramidal neurons in rat neocortex. J. Physiol. 528.3, 489-496, 2000.