

Stochastic fluctuations of the synaptic function

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1. Introduction

The response of single excitatory synapses in hippocampal neurons to a quantal release of neurotransmitters shows a large variability. In a recent paper, Liu *et al.*, 1999, reported that the stimulation of putative single synaptic boutons of hippocampal neurons at excitatory synapses produced quantal Excitatory PostSynaptic Currents (EPSCs) with peak amplitudes having a 5-65 pA range. The histogram of the peak amplitudes showed a long right tail. If the variability of the postsynaptic response observed in hippocampal neurons should be extended to all the neurons of brain, it would constitute a strong biological constraint for all the theories about superior brain functions and, in particular, for the theories on brain neural code. The relatively recent hypothesis assuming that the neural code is embedded in temporally coherent firing events, in a few milliseconds time windows (Abeles, 1991; Hatsopoulos *et al.*, 1998; Riehle *et al.*, 1997), should be faced with this new constraint. The experimental data assert that the peak amplitude of the input arriving in time to a neuron from the same synapse (i.e., from the same linked neuron) is so randomly variable that no precise effect can be attributed to single events. In this instance, a brain neuron would result much more, and subtly, noisy than assumed previously. This urged us to study the synaptic function more deeply by mathematical modeling and computer simulation methods.

We know that the synaptic transmission is driven by a complex chemical machinery involving several, different molecules and structures both at the pre- and postsynaptic side. Diffusion of the neurotransmitter molecules in the synaptic cleft is one of its crucial points that is influenced by the geometry of the synaptic space, both at the presynaptic side and at the postsynaptic one, and by probabilistic factors. The problem of synaptic transmission was discussed in our recent papers where we addressed it by using a Brownian model for diffusion of glutamate molecules in the synaptic cleft (Di Maio and Ventriglia, 2000; Ventriglia and Di Maio, 2000a, 2000b, 2001).

2. Model and Simulation results

The Brownian motion model of synaptic transmission used in the work which constitutes the basis of the present communication was described in our above quoted articles. It is based on appropriate time discretized Langevin equations that were used to simulate the Brownian motion of glutamate molecules both in the synaptic vesicle and in the synaptic cleft. By this model we can simulate the release of glutamate neurotransmitter from a single docked vesicle, the diffusion of neurotransmitter molecules in the synaptic cleft, their binding on postsynaptic receptors, their re-uptake, and their spill over. Our previous studies showed that the number of molecules contained in a vesicle is one of the most important synaptic parameter, hence, it must be carefully computed by experimental data. One of the factor affecting this number is the volume of the vesicle. Shikorsky and Stevens, 1999, computed the size distribution of vesicles by three-dimensional reconstruction of CA1 excitatory synapses. The vesicle diameter varies in a significant range. As a result we have that different spikes, arriving to the same synapse at different times, produce a variable number of

neurotransmitter molecules diffusing within the synaptic cleft. Yet, a second cause of variability is present at the presynaptic side. The docked vesicles are scattered over a, so-called, active zone where they occupy places having different distances from the center. The arrival in time of spikes induces, each one, the formation of a fusion pore between a single vesicle and the presynaptic membrane. Hence, the points from which the neurotransmitter diffusion starts can have different distances with respect to the center of the PostSynaptic Density, where receptors lay. In the present communication we investigated the effects of the volume/position stochastic variability of neurotransmitter vesicle on the postsynaptic response. We analyzed both the sources of variability by several computational experiments. Our results provide evidence that both the factors induce variable EPSC peak amplitudes. Moreover, we demonstrated that the greater part of stochastic variability of EPSC peak amplitudes is to be attributed to the presynaptic machinery.

References

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