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Bilateral processing in chemical synapses with electrical 'ephaptic' feedback: A theoretical model

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Abstract

I have developed a detailed biophysical model of the chemical synapse which hosts voltage-dependent presynaptic ion channels and takes into account the capacitance of synaptic membranes. I find that at synapses with a relatively large cleft resistance (e.g., mossy fiber or giant calyx synapse) the rising postsynaptic current could activate, within the synaptic cleft, electrochemical phenomena that induce rapid widening of the presynaptic action potential (AP). This mechanism could boost fast Ca^{2+} entry into the terminal thus increasing the probability of subsequent synaptic releases. The predicted difference in the AP waveforms generated inside and outside the synapse can explain the previously unexplained fast capacitance transient recorded in the postsynaptic cell at the giant calyx synapse. I propose therefore the mechanism of positive ephaptic feedback that acts between the postsynaptic and presynaptic cell contributing to the basal synaptic transmission at large central synapses. This mechanism could also explain the supralinear voltage dependence of EPSCs recorded at hyperpolarizing membrane potentials in low extracellular calcium concentration.

Keywords: Chemical synapse with 'ephaptic' feedback; Non-linear differential equations; Electrical field

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1. Introduction

Classically, chemical synapses are polarized: they convey information from the presynaptic to the postsynaptic cell. However, retrograde signaling generated in the postsynaptic cell, either by chemical messengers [1–3] or by electric fields [4–6], may influence the functioning of the presynaptic neuron. Retrograde signaling created in the postsynaptic neuron by the electric field, may provide a very fast local activation (positive feedback, [5]) or inhibition (negative feedback, [7]). In the case of positive feedback, the current generated in the postsynaptic neuron would modify transmitter release by directly changing the presynaptic potential at the release site [4,6,8]. The ephaptic feedback should occur mainly in synapses with large synaptic contacts [9]. In accordance with these predictions, it was previously showed that hyperpolarising the postsynaptic neuron produces a supralinear increase in the amplitude of the mossy fiber (MF) EPSCs [5,10]. The increase was stronger than that predicted from the shift in the driving force and was restricted only to large MF inputs to CA3 pyramidal cells (and not to the associative-commissural fiber synapses). Perhaps surprisingly, this supralinear increase was found to correlate with common indicators of the synaptic release probability [10]. However, the biophysical mechanism underlying these phenomena remained largely unexplained [5], in spite of the fact that the paired recording revealed the possible ephaptic connection in hippocampal mossy fiber boutons [11] and at the giant calyx of Held synapse [12]. In such recordings, the ephaptic signals have been seen as either a capacitative transient that precedes the postsynaptic current [12] or a relatively small ephaptic currents in a presynaptic neuron [11]. In addition, the capacitance-coupled activity in the postsynaptic neuron (antidromic ephaptic signal) shows up as a 'postpotential' following the falling phase of the presynaptic spike (see Fig. 4d in [13]).

In the present study, I propose a complex dynamic model of synaptic transmission, which includes the electrical 'ephaptic' feedback between postsynaptic and presynaptic membranes. Parameters and mechanisms used in the model correspond to what has been observed in the giant calyx of Held synapses where ephaptic effects should be particularly strong. The proposed model takes into account (i) the dynamics of calcium concentration in the presynaptic terminal, (ii) the kinetics of vesicle fusion, (iii) glutamate dynamics within the cleft, and (iv) activation of postsynaptic glutamate receptors. My findings extend the conclusions of previous theoretical calculations [14], suggesting that the ephaptic feedback can be sufficiently strong to modulate synaptic efficacy.

2. Methods

2.1. General description of the electrical processes in a chemical synapse

In the scheme of Fig. 1 the simulated synapse is represented. This consists of three parts, the axonal, the pre-, and the postsynaptic areas separated by the synaptic cleft.

The presynaptic part consists of two compartments. The first faces the extracellular space; the second is in front of the synaptic cleft. I shall refer to these two compartments as 'extrasynaptic' (or 'out of the cleft') and 'intrasynaptic' (or 'cleft'), respectively. In the Calyx of Held the surface areas of extra- (S_1) and intrasynaptic membranes are comparable giving $\Delta = S_1/S_2$ close to unity [31]. However, our term 'extrasynaptic membrane' includes extrasynaptic membrane and the