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A computational model of synaptic transmission at the calyx of Held

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Abstract

The calyx of Held is a giant glutamatergic synapse in the mammalian auditory pathway designed to ensure faithful transmission of high frequency action potential trains. Pre- and postsynaptic recordings from this synapse reveal several forms of facilitation and depression. A computational model of synaptic transmission has been developed to investigate the mechanisms underlying modulation at the calyx of Held. The model includes paired-pulse facilitation and depression due to vesicle depletion and postsynaptic AMPA receptor desensitization. Accurately matching the experimental time course and magnitude of the depression requires both slow and fast replenishment of vesicles at the presynaptic release sites. The model demonstrates that the temporal accuracy of postsynaptic spike generation depends on the amplitude of the EPSC and so accuracy decreases as the EPSCs depress.

Keywords: Calyx of Held; Synaptic transmission; Synaptic depression

1. Introduction

The calyx of Held is a giant synapse in the mammalian auditory system designed to ensure faithful transmission of high frequency action potential trains [5,8]. Each calyx

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arises from a single globular bushy cell axon collateral. The bushy cell body receives the excitatory primary afferent projection and is located in the anterior ventral cochlear nucleus (aVCN). The giant synapse forms on the soma of principal neurones in the contralateral medial nucleus of the trapezoid body (MNTB). Each MNTB neurone receives only a single giant synapse. Transmission is glutamatergic and the postsynaptic reponse contains both AMPA and NMDA receptor-mediated components. Several hundred presynaptic release sites ensure large postsynaptic EPSCs that will fire an action potential in the MNTB neurone for each presynaptic action potential. Fast sodium and potassium currents ensure that the postsynaptic action potential train follows a presynaptic train on a one-for-one basis, even at frequencies of several hundred per second [4,13].

Experimentally, this synapse allows simultaneous pre- and postsynaptic recording [5]. This, combined with the lack of electrotonic distortion of the postsynaptic EPSCs (as they are all generated at the soma), provides an exceptional view of synaptic transmission at a central mammalian synapse. The picture that is emerging reveals a variety of forms of facilitation and depression. We have developed a computational model of this synapse to enable us to investigate how the interaction of different mechanisms results in the modulation of synaptic transmission and the postsynaptic response.

2. The model

An *intermediate level* computational model of this synapse has been developed using biophysically-based components represented in simple ways. Arrival of a presynaptic action potential (AP) results in fast (Ca_f) and slow calcium (Ca_s) transients that drive vesicle release and replenishment, respectively, for 500 independent release sites (Fig. 1).

The probability of release (R) is determined by the product of the open states of two gates which open and close at different rates in the presence of calcium [3]. The fast gate rapidly opens and closes during the fast calcium transient ($Ca_f = 0.1$ mM for 1 ms) following an action potential. The slow gate opens less, but closes slowly so that it may still be partially open when the next action potential arrives, leading to potentiation of the probability of release for that action potential. Such facilitation occurs for interspike intervals of 10 ms or less. Release of a vesicle results in a 1 ms pulse of 1 mM neurotransmitter, T, that produces an AMPA receptor-mediated EPSC which includes receptor desensitization [7]. There is constant background replenishment of vesicles from a large reserve pool, S, and frequency-dependent replenishment driven by the slow (residual) calcium transient ($Ca_s = 0.01$ mM for 2 ms). Replenishment rates are sufficiently slow that depletion of vesicles and subsequent depression of the EPSC occurs at even low frequencies of stimulation (e.g. 0.5 Hz). In some situations, fast sodium and potassium channels [2] were added to the postsynaptic cell to produce action potentials in response to the EPSCs.

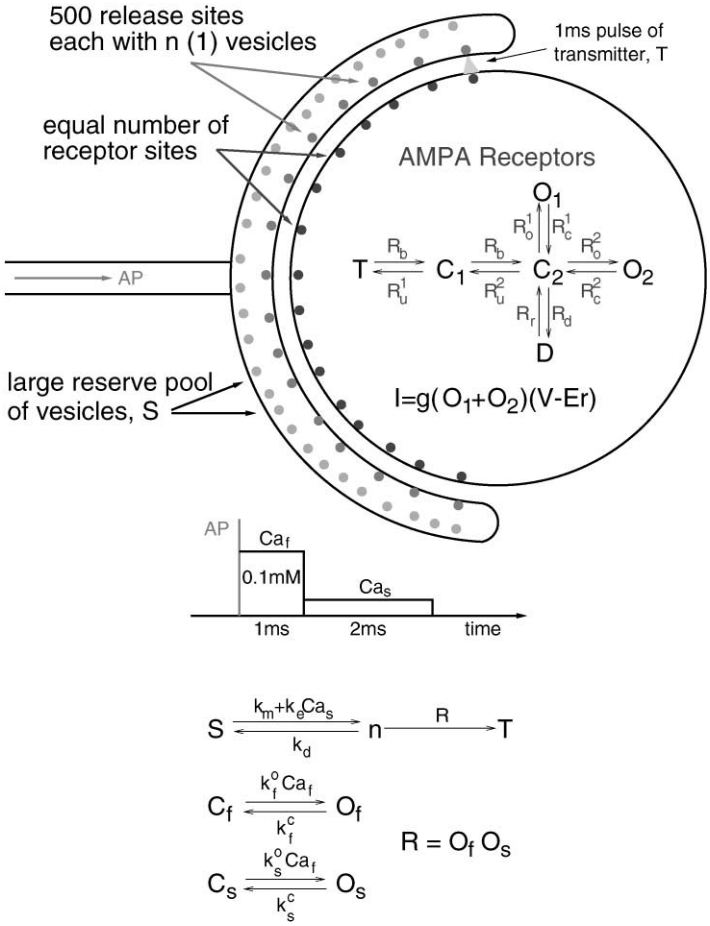

Fig. 1. Computational model of the calyx of Held. Unless otherwise specified, parameter values were: $k_m = k_d = 0.2$/s, $k_e = 8$/mM-ms, $k_f^o = 150$/mM-ms, $k_f^c = 30$/ms, $k_s^o = 1$/mM-ms, $k_s^c = 0.1$/ms, $R_b = 13$/mM-ms, $R_u^1 = 0.3$/ms, $R_u^2 = 200$/ms, $R_d = 30$/ms, $R_r = 0.02$/ms, $R_o^1 = 100$/ms, $R_c^1 = 2$/ms, $R_o^2 = 2$/ms, $R_c^2 = 0.25$/ms, $g = 500$ pS, $E_r = 7$ mV. When postsynaptic Na and K channels included, cell diameter = 20 μm, $R_m = 500\,\Omega\,\mathrm{cm}^2$, $C_m = 1\,\mu\mathrm{F/cm}^2$, $\bar{g}_{\mathrm{Na}} = 25\,\mathrm{mS/cm}^2$, $\bar{g}_{KDR} = 30\,\mathrm{mS/cm}^2$. The model was simulated using *NEURON* [6].

3. Results

The model reproduces experimental results for the time course and magnitude of depression of EPSCs in response to trains of presynaptic action potentials (APs) (Fig. 2). Depression is largely due to depletion of vesicles and its magnitude is determined by the rate of vesicle replenishment. Experimental data show either near complete depression (Wong and Forsythe, unpublished) or an elevated steady-state

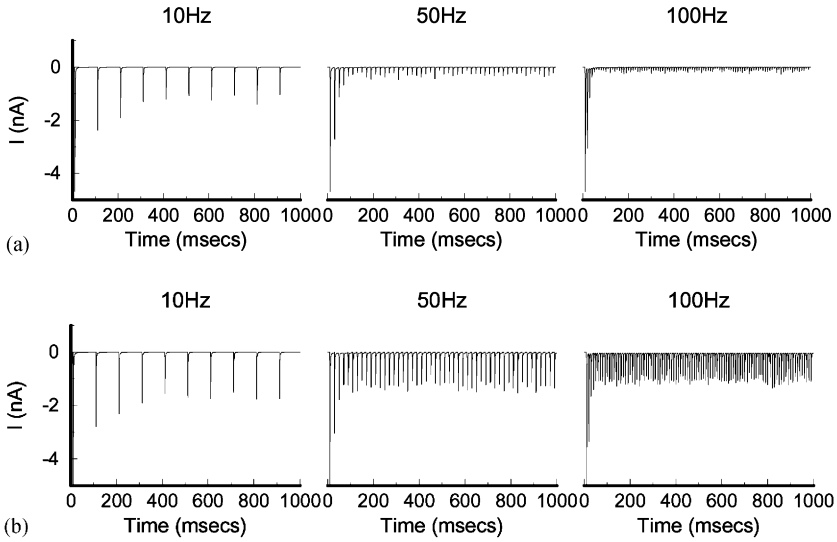

Fig. 2. Examples of EPSCs. Upper traces: background replenishment of vesicles is high, but there is no frequency-dependent replenishment ($k_d = 1.5$/s, $k_e = 0$). Lower traces: rate of vesicle replenishment is frequency-dependent.

EPSC amplitude [9,10]. In the model, such elevation is due to frequency-dependent replenishment of vesicles, as proposed for the neuromuscular junction [11,12].

A simple model of replenishment [12] indicates that the steady-state postsynaptic response becomes largely frequency-independent for presynaptic frequencies in the 10 Hz Hertz and above. Experiments from the calyx of Held show a continuing depression of the steady-state EPSC amplitude up to 300 Hz [10]. In our model, AMPA receptor desensitization causes an extra frequency-dependent depression of the postsynaptic response.

Triplet responses may show continuing depression, facilitation followed by depression or continuing facilitation, depending on the extracellular calcium concentration [1]. In the model, these different triplet responses arise from the relative rates of facilitation of the probability of release and depletion of vesicles (Fig. 3). High external calcium results in a high release probability and rapid depression due to vesicle depletion. At lower release probabilities (lower external calcium), sufficient docked vesicles may still be available for subsequent action potentials that facilitation may result in a larger response to the second action potential than to the first.

Adding fast sodium and potassium channels to the postsynaptic cell allows investigation of the properties of the postsynaptic spike train that results from the EPSCs. Fig. 4 indicates that depression of the EPSCs affects the temporal accuracy of postsynaptic AP generation. As the presynaptic response depresses, the delay in postsynaptic spikes increases from 1 to 1.5 ms and the variance in spike times increases 5-fold.

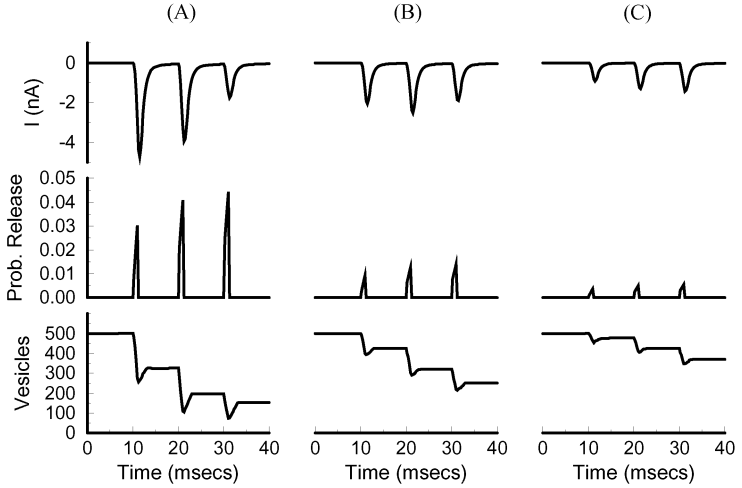

Fig. 3. Examples of triplet responses at 100 Hz. Top traces show EPSCs, middle traces show time course of probability of release, R and lower traces show total number of readily releasable vesicles in the calyx. (A) fast calcium transient has amplitude of 0.1 mM, generating an R that results in about 50% of vesicles releasing on the first action potential. (B) Ca_f amplitude reduced to 0.05 mM. (C) Ca_f amplitude reduced to 0.03 mM.

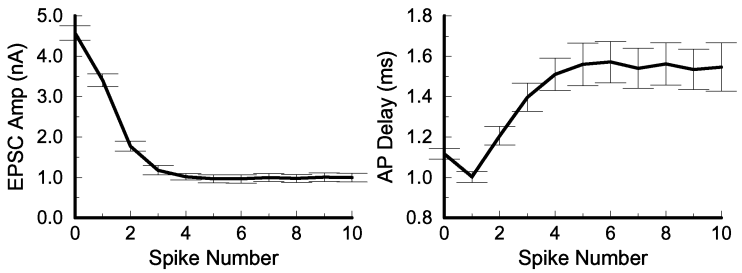

Fig. 4. EPSC amplitude and resultant postsynaptic AP delay at 100 Hz (error bars are std. dev.).

4. Conclusions

The calyx of Held exhibits depression of EPSCs due to depletion of vesicles. However, frequency-dependent replenishment of readily-releasable vesicles can maintain EPSC amplitude sufficiently for a postsynaptic spike to be produced for each presynaptic spike even at high frequencies. Why, then, should the initial EPSC in a train be so large? Our simulations demonstrate that this large EPSC at the onset of a new stimulus produces a temporally accurate postsynaptic spike that is suitable for use in determining an interaural time difference (ITD). The smaller EPSCs that follow produce less temporally accurate spikes, but these are likely sufficient for calculation

of the interaural level difference (ILD). Thus all EPSCs are only as large as they need to be, minimizing the usage of vesicles.

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