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A multi-component model of depression at the calyx of Held

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Abstract

An average-response model of depression at the calyx of Held, a giant glutamatergic synapse in the mammalian auditory pathway, is presented. The model is fit to experimentally recorded EPSC amplitudes resulting from 10 to 100 Hz presynaptic stimulation for 1 s. This data exhibits a strong depression of the EPSC amplitude. The model best fits the time course and magnitude of depression when significant postsynaptic receptor desensitisation and vesicle replenishment from a small, depleting reserve pool were included.

Keywords: Calyx of Held; Synaptic transmission; Synaptic depression

1. Introduction

The characteristic postsynaptic response to trains of presynaptic action potentials at the calyx of Held is a rapid depression of the EPSC amplitude to a non-zero steady-state value. The major component of this depression is depletion of the releasable presynaptic vesicles. The slow replenishment (time constant of around 5 s) of the readily-releasable vesicle pool (RRVP) should result in an essentially zero steady-state EPSC amplitude at high frequency stimulation (>10 Hz). The non-zero steady-state amplitudes after stimulation for 1–2 s seen experimentally indicate a faster time constant for vesicle replenishment during presynaptic activation. The precise mechanism underlying such fast replenishment is unknown. The data can be fit by a simple activity-dependent model

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[1], but residual calcium as the underlying driving force is not supported by experiment and further modelling work [5]. A two-pool model in which one vesicle pool is replenished substantially faster than the other provides intrinsic activity-dependent replenishment and fits some data [3]. Recent experimental and modelling work indicates a significant contribution of postsynaptic receptor desensitisation to the steady-state EPSC amplitude at frequencies above 10 Hz [6].

In this paper we explore the contributions of vesicle depletion and recycling and postsynaptic receptor desensitisation to depression of the EPSC amplitude during high frequency stimulation at the calyx of Held. A model is fit to the average EPSC amplitudes during stimulus trains obtained experimentally. The best fit to the data is obtained when vesicle replenishment is activity-dependent from a finite-sized reserve pool. Desensitisation contributes both to the time course of depression and the steady-state EPSC amplitude at high frequency stimulation.

2. The model

The calyx of Held consists of hundreds of active zones operating in parallel and possibly independently. The model we propose describes the average postsynaptic response at this synapse as a function of time and presynaptic stimulation. Similar models have been used to describe synaptic transmission at a variety of central synapses [4] and at the neuromuscular junction [7]. Novel features here are an explicit desensitisation of postsynaptic receptors and presynaptic vesicle recycling from a finite-sized reserve pool.

The presynaptic response to an action potential is determined by the availability of vesicles at each release site within an active zone and their probability of release. The model assumes a uniform release probability for all vesicles in an active zone, with vesicles arriving at an active zone and becoming release-ready at a rate that is a function of presynaptic stimulus frequency. This activity-dependent recycling model has previously been proposed to describe facilitation of release at the neuromuscular junction [7]. Here, however, we consider vesicle recycling from a finite-sized reserve pool that is sufficiently small so as to affect recycling rates as it becomes depleted. The time evolution of the availability of releasable vesicles is given by

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \frac{(1-n)}{\tau_n} + (n_\mathrm{s} n_\mathrm{r} - P_\mathrm{v} n)\delta(t - t_\mathrm{s}), \tag{1}$$

$$\frac{\mathrm{d}n_\mathrm{r}}{\mathrm{d}t} = -n_\mathrm{r}\frac{n_\mathrm{s}}{n_\mathrm{r}^0}\delta(t - t_\mathrm{s}), \tag{2}$$

where n is the average number of releasable vesicles available per release site ($n = 1$ corresponds to every site being filled with a releasable vesicle). On the arrival of a presynaptic spike at time t_s, a vesicle may release with probability P_v, and a fraction n_s of vesicles from the finite-sized reserve pool, which initially contains n_r^0 vesicles, is mobilised to replenish each site. The fraction of vesicles remaining in the reserve pool is given by n_r. Recovery of this reserve pool is assumed to be sufficiently slow that it is essentially zero during the time course of the stimulus trains considered here.

In addition, there is background replenishment of release sites from an assumed very large reserve pool with time constant $\tau_n = 5$ s. The average release from each site at the time of arrival of a spike is:

$$P_r(t_s) = P_v n(t_s). \tag{3}$$

The amplitude of the postsynaptic response depends both on the probability of vesicle release and the state of the postsynaptic receptors. Following the binding of neurotransmitter, the receptors may desensitise and are not again available for contributing to the postsynaptic response until they recover. The average receptor desensitisation is given by

$$\frac{dr_d}{dt} = -\frac{r_d}{\tau_d} + DP_r(1 - r_d)\delta(t - t_s). \tag{4}$$

D is the fraction of receptors that instantaneously enter the fast desensitised state on the binding of neurotransmitter and τ_d specifies their rate of recovery.

The average amplitude of the postsynaptic response is the product of the number of released vesicles and the available (nondesensitised) receptors:

$$PSR(t_s) = P_r(t_s)(1 - r_d(t_s)). \tag{5}$$

The model has been implemented in Matlab, and also in NEURON, in which the Praxis optimisation package was used to optimise model parameters against experimental data.

3. Results

In experiments at the calyx of Held [6], the postsynaptic EPSC amplitude shows a significant depression when subject to regular presynaptic stimulation at 10, 20 and 50 and 100 Hz for 1 s. The response of the model, optimised against this data, is shown in Fig. 1. Both model and experimental data are plotted normalised against

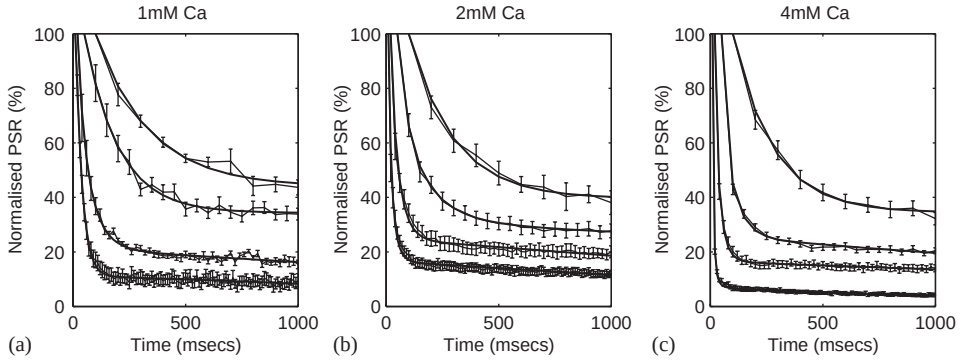

Fig. 1. Depression of the postsynaptic response with regular presynaptic stimulation at 10, 20, 50 and 100 Hz (from top to bottom) in (a) 1, (b) 2 and (c) 4 mM external calcium. ($\tau_n = 5$ s; $D = 1$; P_v, n_s, τ_d and n_r^0 optimised against the data.)

the amplitude of the first response in a train. In most cases, both desensitisation and a finite-sized reserve pool were required in the model to get an accurate fit to the time course and magnitude of depression. At 10 Hz stimulation, the data was well fit with no desensitisation, and a reserve pool sufficiently large that depletion of the pool was not a factor over the 1 s stimulation period. This also applied at 20 Hz in the low release conditions of 1 mM external calcium. For the remaining data, inclusion of significant desensitisation and a small reserve pool, initially containing from 9 to 26 vesicles per active zone, significantly improved the fit of the model. Depletion of the small reserve pool adds a very slow component to the depression which matches the rundown in EPSC amplitude apparent particularly at 50 and 100 Hz stimulation.

The optimised values for the model parameters P_v, τ_d, n_s and n_r^0 are shown in Fig. 2. As expected, there is a trend of increasing release probability with increasing external calcium. The activity-dependent vesicle recycling rate also appears to increase with external calcium. Desensitisation contributes less to depression in the low release conditions of 1 mM calcium. A small improvement in model fit to the 50 and 100 Hz data in these conditions was obtained but only with a longer time constant for recovery

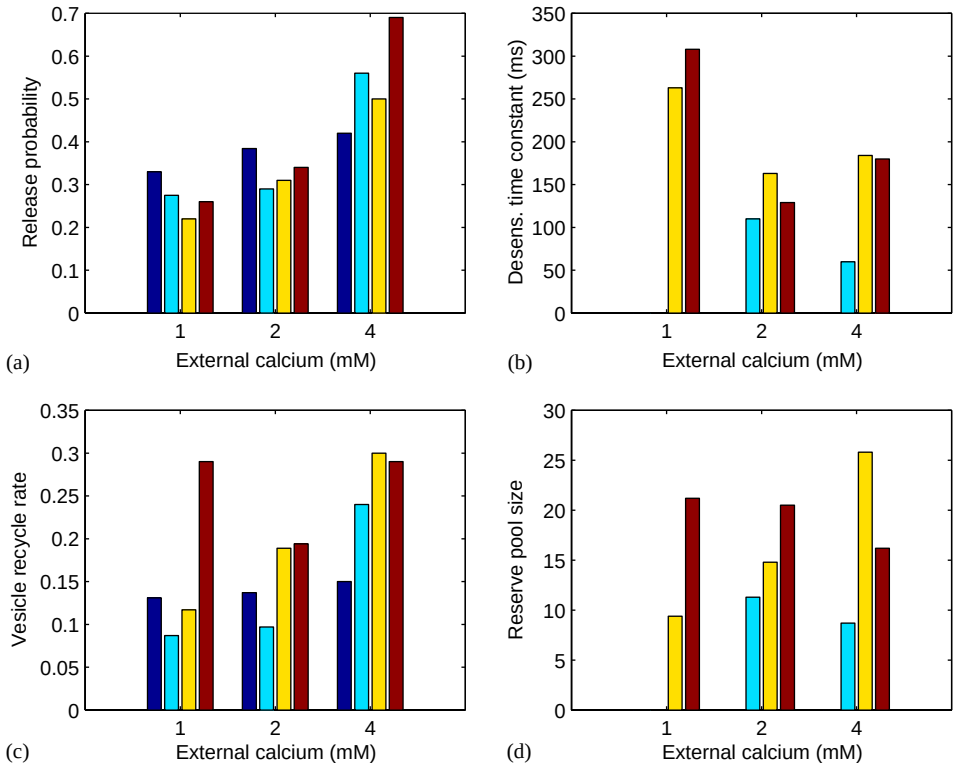

Fig. 2. Optimal values for (a) release probability (P_v), (b) desensitisation recovery time constant (τ_d), (c) vesicle recycling rate (n_s) and (d) initial reserve pool size (n_r^0) at 10, 20, 50 and 100 Hz (left-to-right at each calcium level).

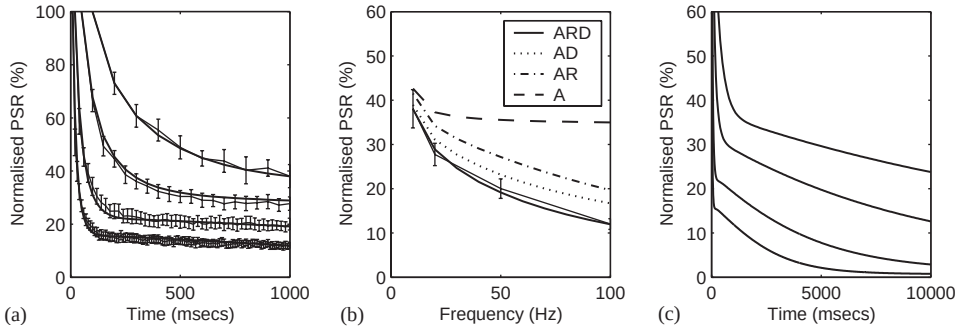

Fig. 3. Response of the canonical model: (a) Postsynaptic response to regular presynaptic stimulation at 10, 20, 50 and 100 Hz (top to bottom). (b) Relative amplitude of EPSC after 1 s as a function of stimulation frequency (ARD—full canonical model; AD—no rundown of reserve pool; AR—no desensitisation; A—no rundown or desensitisation). (c) As for (a) but stimulation for 10 s. ($P_v = 0.27$, $\tau_n = 5$ s, $D = 1$, $\tau_d = 121$ ms, $n_s = 0.093$ and $n_r^0 = 15$.)

from desensitisation than obtained in higher release conditions. There is little discernible trend in any of the parameters with the frequency of stimulation.

The response of a canonical model, determined by optimising the parameters against the 2 mM calcium data for all frequencies simultaneously, is shown in Fig. 3. The data is still well fit at all frequencies (Fig. 3(a)). The prominent role of desensitisation in determining the amplitude of depression is highlighted in Fig. 3(b). With no desensitisation and no rundown of the reserve pool, the depression amplitude after 1 s stimulation is independent of frequency. The effect of vesicle reserve pool rundown is much more significant when there is no desensitisation. Rundown of the finite-sized reserve pool eventually leads to near complete depression at all frequencies above 10 Hz (Fig. 3(c)). This rundown takes around 50 s at 10 Hz, down to 5 s at 100 Hz.

4. Conclusions

This model is sufficient to capture the major characteristics of the amplitude and time course of depression at the calyx of Held [6]. It reveals the apparent contribution of a number of different factors to the depression of the EPSC amplitude at stimulation by high frequency action potential trains (> 10 Hz). Desensitisation plays a significant role in both the time course and magnitude of depression. Even after 1 s stimulation, there is some rundown in the steady-state depression level at 50 and 100 Hz. We account for this by depletion of a small vesicle reserve pool that contributes to activity-dependent replenishment of release sites during stimulation. Small numbers of undocked vesicles close to release sites have been observed in calyx-type synapses [2].

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