A biophysical model of short-term plasticity at the calyx of Held

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Abstract

The calyx of Held is a giant glutamatergic synapse in the auditory system and displays multiple forms of short-term facilitation and depression. This study presents a detailed model of short-term plasticity at this synapse. The main components of the model are the presynaptic vesicle dynamics, which include passive and activity-dependent recycling, calcium-dependent exocytosis and the postsynaptic AMPA receptor kinetics. The behaviour of the model is compared to experimental data and reproduces the time course and amplitude of synaptic depression during repetitive stimulation at different frequencies. A comparison of different manipulations of the model shows that accurate fits require the inclusion of fast activity-dependent vesicle recycling and a limited number of vesicle docking sites at each active zone.

Keywords: Calyx of Held, Synaptic transmission, Synaptic depression, Model

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1 Introduction

Short-term plasticity (STP) is a general feature of synapses and has been intensively studied in many different preparations [1]. During repetitive stimulation a postsynaptic response can be facilitated or depressed or modulated by a combination of both, and typically factors such as stimulus frequency and history influence the precise modulation characteristics.

In this study, STP was investigated at the calyx of Held, a giant glutamatergic synapse located in the medial nucleus of the trapezoid body (MNTB; [2]). The calyx is an important model system for STP because only a single afferent axon synapses onto a postsynaptic neuron, and both pre- and postsynaptic events can be recorded simultaneously. Its predominant feature is strong stimulus-dependent depression, which is influenced by both pre- and postsynaptic factors. Earlier work has led to the vesicle depletion model for short-term synaptic depression based on the activity-dependent depletion of release-ready vesicles [3], which can explain aspects of STP at the calyx of Held [4, 5].

On the other hand, it is known that a variety of mechanisms acting at different sites and time scales contribute to STP at the calyx of Held. These include AMPA receptor (AMPAR) desensitisation [5], voltage gated calcium channel (VGCC) inactivation [6] and facilitation [7, 8] and activation of presynaptic metabotrophic glutamate receptors (mGluRs), which suppresses calcium currents [9, 10]. In this work, these mechanisms were combined in a detailed model of synaptic transmission, which was then directly compared to experimental data. This model significantly alters and extends our previous models [10, 11].

2 The Model

All processes were implemented by coupled linear differential equations, and the results shown here were obtained by numerical integration of the deterministic model. A schematic illustration of the model is given in Figure 1. The model has a presynaptic compartment, where vesicular glutamate release occurs after arrival of an action potential (AP), and a postsynaptic compartment, where the current response is generated by AMPARs.

In the presynaptic compartment, transmitter release depends on the occupancy of the pool of releasable vesicles $n(t)$ and the probability of transmitter release $p(t)$. The average amount of transmitter released after an AP is then given by $T(t)$=$n(t)\cdot p(t)$.

The model of the vesicle dynamics assumes that two different vesicle pools exist, one large (infinite) reserve pool and a small release-ready vesicle pool. Released vesicles are constantly exchanged with the reserve pool at a rate k_r and replenished by a calcium-dependent process following a presynaptic AP [12] with a constant increment n_e:

$$\frac{dn(t)}{dt} = (1 - n(t)) \left[\frac{1}{\tau_r} + n_e \cdot \delta(t - t_s) \right] - T(t) \cdot \delta(t - t_s). \quad (1)$$

The pool was modelled as a continuous variable (where $n(t)$= 1 corresponds to all available sites containing a docked vesicle) as it is known to be very large at the calyx of Held (1800-3000 vesicles [13]). Due to the factor $(1 - n(t))$, equation 1 models a release pool with a limited size, i.e. release sites have a limited number of "docking" sites for vesicles.

The release probability $p(t)$ depends on the presynaptic $[Ca^{2+}]_i$ according to a power law [14] and is calculated by

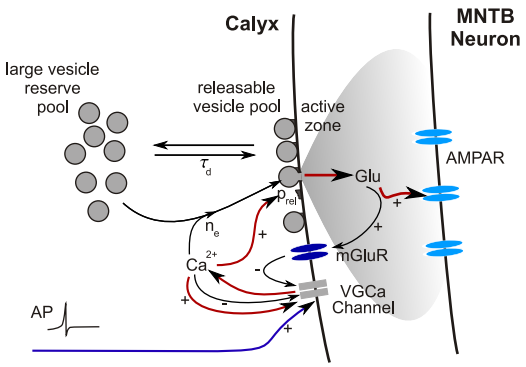

Figure 1: Schematic illustration of the model. For details, see the main text.

$$p(t) = 1 - \exp(-k \cdot ([Ca^{2+}]_i)^{\alpha}), \tag{2}$$

where k is a scaling factor and α the exponent that relates the calcium concentration with the release rate.

The amplitude of the AP-evoked calcium transient $[Ca^{2+}]_i$ is variable due to inactivation [6] and facilitation [7, 8] of calcium channels and their suppression due to activation of presynaptic mGluRs [9]. This was modelled by the following set of equations:

$$\frac{dc_1(t)}{dt} = \frac{c_2(t) - c_1(t)}{\tau_f} + n_f \cdot \delta(t - t_s) \tag{3}$$

$$\frac{dc_2(t)}{dt} = \frac{i(t)}{\tau_i} + \frac{b(t)}{\tau_b} - [n_i + n_b \cdot T(t)] \cdot c_2(t) \cdot \delta(t - t_s) \tag{4}$$

$$\frac{di(t)}{dt} = -\frac{i(t)}{\tau_i} + n_i \cdot c_2(t) \cdot \delta(t - t_s) \tag{5}$$

$$\frac{db(t)}{dt} = -\frac{b(t)}{\tau_b} + n_b \cdot T(t) \cdot c_2(t) \cdot \delta(t - t_s) \tag{6}$$

The variable c_1(t) (Eqn. 3) describes the evolution of the amplitude of $[Ca^{2+}]_i = C_0 \cdot c_1(t)$, and models calcium channel facilitation by increasing c_1(t) by a constant amount n_f after each presynaptic AP, which decays with τ_f to c_2(t). c_2(t) accounts for the suppression of the calcium current by inactivation and mGluR activation in Equations 4-6. Here it was assumed that calcium channels can reversibly switch from a resting (c_2) to an inactivated (i) or blocked state (b). The blocked state represents a simple model of the effect of presynaptic mGluRs on calcium channels [10] and the forward rate therefore depends on the amount of released transmitter $T(t)$. The constants n_i and n_b define the rates into, and time constants τ_i and τ_b the recovery from the inactivated and blocked states, respectively.

Finally, the postsynaptic response is affected by AMPAR desensitisation [5]. This was modelled assuming a reversible transition into a desensitised state with an increment n_d and recovery time τ_d:

$$\frac{dD(t)}{dt} = -\frac{D(t)}{\tau_d} + (1 - D(t)) \cdot n_d \cdot T(t). \tag{7}$$

The postsynaptic response was then calculated according to $R(t) = T(t) * (1 - D(t))$.

Parameter	Value	Parameter	Value
τ_r	2.5s	n_e	0.056
n_f	0.091	τ_f	0.0252s
n_i	0.003	τ_i	8s
n_b	0.21	τ_b	0.6s
C_0	0.034mM	k	193200
α	4		
n_d	3.3	τ_d	0.05s

Table 1: Parameters used in the simulations.

All parameters used in the simulations shown here are summarised in Table 1. All simulations were performed in Matlab, and the code is available from the authors upon request.

3 Results

This model was assessed by simulating EPSCs in response to trains of presynaptic action potentials at different stimulus frequencies. Figure 2A shows the time course of depression for four different frequencies obtained in simulations (black lines) in comparison with experimental data (grey lines).

The experimentally obtained responses (Fig.2A, grey lines) show that depression has two distinct phases: a rapid reduction of the response followed by a slow rundown, which is clearly visible in the double-logarithmic representation (Fig.2A2, arrow). The latter feature is especially visible at high stimulus frequencies and consistently carries on in longer recordings (MP and IDF, unpublished data). This indicates that multiple mechanisms, acting on different time scales, interact at the calyx of Held. This behaviour can be reproduced with the model and is a consequence of the interaction of vesicle pool depletion and AMPAR desensitisation on the one hand, which act on fast time scales, and of calcium channel inactivation and mGluR activation on the other, which act on much slower time scales (Fig.2B, also compare rates and time constants in Table 1).

A key assumption in the model is that the number of vesicles recycled after an AP depends on the *occupancy* of the release sites ($(1-n(t))\cdot n_e$). Hence it assumes a limited number of sites for vesicle docking at an AZ. In the alternative model, assuming an unlimited release pool, the factor $(1-n(t))$ disappears in the limiting case of a very large reserve pool. The behaviour of the latter model is shown in Figure 2C (black traces). Only in the occupancy-dependent model a slow rundown of activity can be observed at high frequencies (arrows in Fig.2A2 and D). The reason for this different behaviour is a different steady-state behaviour ($t \to \infty$). With an unlimited release pool, changes in $p(t)$ are instantly compensated by vesicle recycling, as $n(t)p(t) = n_e$ is constant [10]. With a pool of fixed size, this changes to $n(t)p(t) = n_e \cdot (1-n(t))$, hence changes in $p(t)$ are not fully compensated by vesicle recycling. This is illustrated in Figures 2C and 2E, which show a reduced rate of vesicle recycling at high frequencies when the release pool was kept limited.

4 Discussion

In this paper we present a model that can reproduce the dynamics of synaptic depression at the calyx of Held at different frequencies. It is consistent with the concept that vesicle pool depletion strongly contributes to synaptic depression. In addition, however, the comparison of experimental data with simulated responses

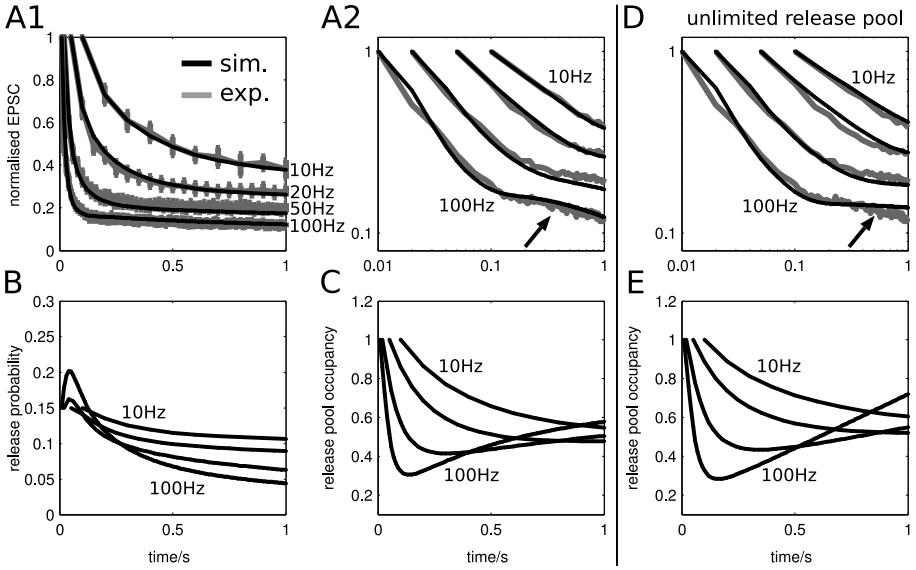

Figure 2: Simulation of synaptic depression at the calyx of Held during repetitive stimulation at 10, 20, 50 and 100Hz. A, Normalised simulated (black) and experimental postsynaptic responses (grey, recorded in rats aged P10-P12; for details on the experimental procedures see [5]), plotted in linear (A1) and double-logarithmic (A2) coordinates. B, Temporal evolution of the release probability, C, Temporal evolution of the release pool occupancy. D,E, as A2 and C, but simulated with an unlimited number of release sites. In these simulations, n_e was decreased by a factor of 0.6 to fit the experimental data at 10Hz. Arrows in parts A2 and D indicate the main difference in the behaviour of the two models.

showed that additional mechanisms such as calcium channel inactivation and autoreceptor activation, acting on slower time scales, also contribute. The simulations further suggest the releasable vesicle pool at the calyx of Held has a strictly limited size. This assumption is compatible with the existence of specialised sites, abundant of SNARE proteins, in the presynaptic membrane that allow vesicle docking and fusion[15].

The model presented here may be equally applicable to other synapses. Typically however, the release pool of most synapses is much smaller than that of the calyx of Held [1], such that the variable describing the pool occupancy ($n(t)$) has to be discretisised, which may affect the dynamics of transmission. In addition, depression due to rapid depletion of a smaller release pool will probably mask the calcium-dependent effects in typical paired-pulse protocols or during tetanic stimulation. This model however suggests that these will still contribute to the STP dynamics. It will therefore be an important question for future work how the interaction of multiple mechanisms at synapses will influence synaptic transmission and processing of sensory signals.

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Figure 3: Matthias Hennig is currently MRC fellow at the Institute for Adaptive and Neural Computation, School of Informatics, Edinburgh University, UK. He completed his undergraduate studies in Physics in Bochum, Germany and then received his PhD in Psychology in 2005 from Stirling University, UK. He then held a postdocoral post in the Group of Bruce Graham in the Department of Computer Science at Stirling University, UK.

Figure 4: Michael Postlethwaite is a researcher at the department of Cell Physiology and Pharmacology, University of Leicester, UK. He received his PhD in 1999 from the School of Pharmacy in London, and has since been carrying out electrophysiology and imaging in neurones. He was recently invited to an assistant professorship at the University of Nottingham campus in Malaysia.

Figure 5: Ian Forsythe holds the Chair of Neuroscience and leads the Cellular & Molecular Neuroscience group at the Medical Research Council's Toxicology Unit within the University of Leicester, UK. He received his PhD from the University of Southampton in 1983, held postdoctoral posts at the ANU, Canberra, Australia and at NICHD, NIH, Bethesda, before returning to the UK and Leicester in 1988.

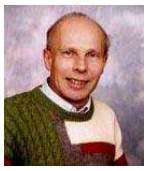

Figure 6: Dr Bruce Graham is a Reader in Computing Science at the University of Stirling, Scotland where he runs a research group in computational neuroscience. He has a PhD in chemical engineering (fuzzy control) from the University of Queensland. He researched computational neuroscience in the labs of Prof. Steven Redman (Canberra) and Prof. David Willshaw (Edinburgh) before moving to Stirling in 2000.