Synapse parameters at the calyx of Held during high and low presynaptic glucose concentration

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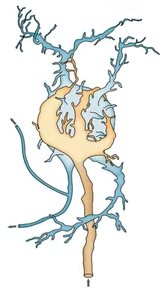
Introduction

To evaluate the effects of changes in presynaptic ATP on synaptic short term plasticity, a mathematical model was developed to model postsynaptic EPSC amplitude changes in response to trains of presynaptic action potential waveforms at the calyx of Held and under conditions of high and low glucose concentrations.



Synapse model

The model is based on an existing model describing the interactions between multiple sources of short-term plasticity during evoked activity (Hennig *et al.*, J. Physiol., 2008). The releasable vesicle pool was modelled as a continuous variable n(t), with n(t)=1 corresponding to all available sites containing a docked vesicle, its dynamics is defined by:

$$\frac{dn(t)}{dt} = \frac{n_{max} - n}{\tau_r} - \sum_j \delta(t - t_j).p.n(t)$$

n_{max} is assumed to decrease (from a starting value of 1) during the late phase of depression (10 secs onwards) and this is modelled with a logistic equation (sigmoid), applied as a decline in available release sites due to lack of ATP during the stimulation:

$$n_{max} = A_n + (1 - A_n) / (1 + e^{-(t - t_n)/k_n})$$

The increases in release probability, due to calcium channel facilitation, accumulation of residual calcium, and the effect of calcium buffers are modelled by:

$$\frac{dp(t)}{dt} = \frac{c(t) - p(t)}{\tau_f} + \sum_j \delta(t - t_j).S_p.k_f.(1 - p(t))$$

The variable c(t) (initialized to p_0) accounts for the slower depressing effects, calcium channel inactivation and calcium channel suppression due to activation of G-proteins, for instance by presynaptic mGluR or AMPAR autoreceptors:

$$\frac{dc(t)}{dt} = \frac{S_p.p_0 - c(t)}{\tau_i} - \sum_j \delta(t - t_j).k_i.c(t)$$

EPSC variance study shows p varies sigmoidally during the low glucose experiments, so a sigmoidal decrease is applied to both facilitation and slow component of the release probability:

$$S_p = A_p + (1 - A_p) / (1 + e^{-(t - t_p)/k_p})$$

Experimental recordings

Recordings have been made from p9-p10 CRA mice in whole cell patch clamp in high (control) and low glucose conditions. The EPSCs were recorded from MNTB neurons voltage-clamped at -40 mV. For postsynaptic recordings a bipolar stimulating electrode was positioned at the midline and given high frequency stimulation (HFS; 100 Hz for 30 s) followed by recovery pulses over a further 20 s. This protocol was given 10 min after a change in the aCSF composition and then repeated every 5 mins. Stimulation voltage was twice the voltage threshold required to evoke an EPSC.

EPSC amplitude variances

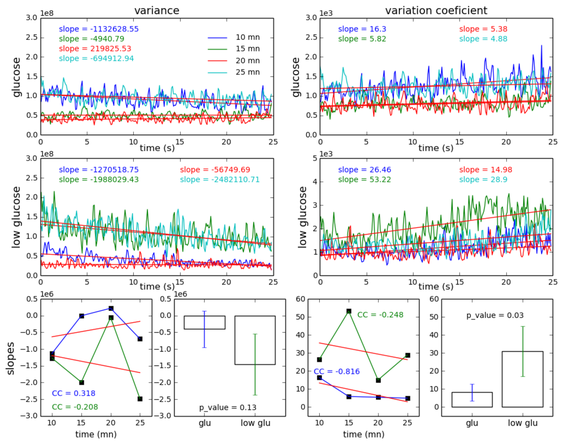
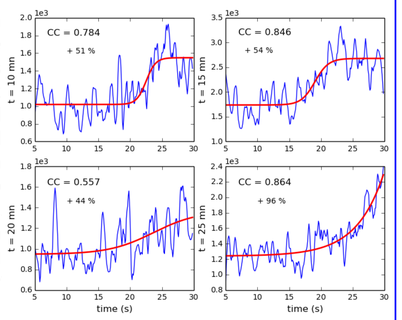


Figure 1: EPSC amplitude variance and coefficient of variation (CV) study. EPSC amplitude variance is proportional to np(1-p), and CV to np(1-p)/np = (1-p). Here the variance and CV are calculated in moving time windows along the final 25 s of 100 Hz stimulation. The change (slope) in Var and CV during HFS are not dependent of the time between recordings. CV is significantly different between high and low glucose experiments, so p is modified by the lack of glucose. Meanwhile variances are not significantly different, suggesting there is also a variation of n between high and low glucose experiments.

Fitting of EPSC cv

Figure 2: CV fitting in low glucose conditions. Changes in CV during 100 Hz stimulation are well fitted by sigmoid curves. Hence such curves are used to model an extra component in changes in p during the stimulation in low glucose.



Model fit to recordings

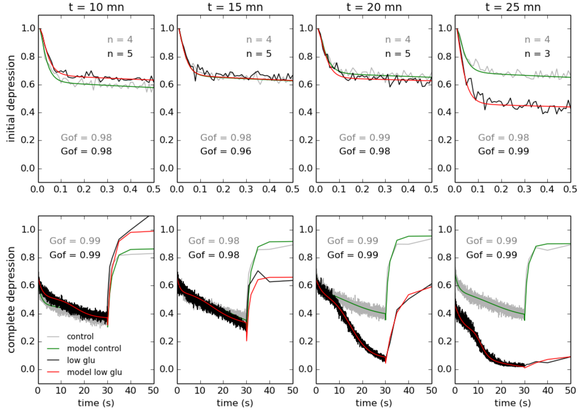


Figure 3: Model fit to experimental recordings of stimulation+recovery, made at 10, 15, 20 and 25 minutes in control (high glucose) or impaired (low glucose) conditions. Upper panels: initial depression, from 0 to 500 ms. Lower panels: complete stimulation protocol with recovery. Controls are shown in grey and responses with low glucose are shown in black. The experimental data are the average of four cells in control conditions and six cells in low glucose conditions.
Note increased depression and impaired recovery in low glucose conditions.

Parameter identification

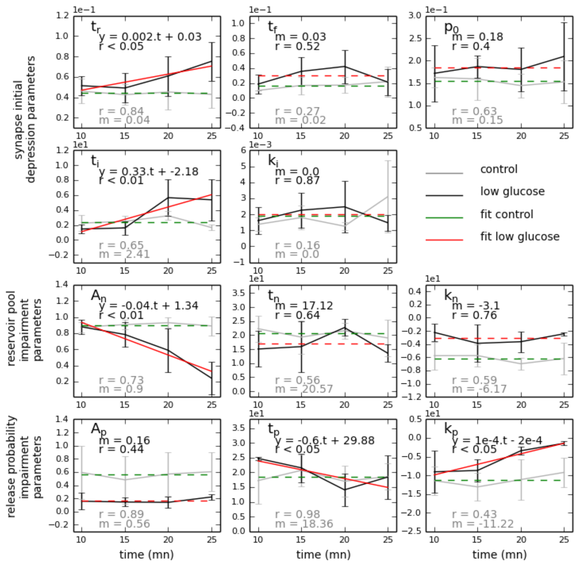


Figure 4: Model parameter estimation for each experimental recording, in control conditions (grey lines) and with low glucose (black lines). In control conditions, none of the parameters evolve against time over the 5 min experimental epochs. In low glucose conditions the vesicle replenishment (tr) and the slow release depression (ti) time constants increase. Also n_{max} decreases (sigmoid offset (A_n) decreases strongly), and the p sigmoid half activation decreases and the slope increases. Thus both n and p are significantly impaired in low glucose conditions.

Summary

Repeated high frequency stimulation in low glucose conditions (resulting in impaired ATP) results in increased EPSC depression during the stimulation and impaired recovery. The model and data analysis predict that the increased depression is due to a decline in vesicle release probability and the size of the readily releasable vesicle pool. Short-term depression indicates the p recovers between 5 min epochs, but EPSC amplitude does not fully recover due to a decline in the number of functional release sites.

Reference

Hennig MH1, Postlethwaite M, Forsythe ID, Graham BP. J Physiol. 2008 Jul 1;586(13):3129-46. doi: 10.1113/jphysiol.2008.152124. Epub 2008 May 1. Interactions between multiple sources of short-term plasticity during evoked and spontaneous activity at the rat calyx of Held.