Extracellular Calcium Depletion as a Mechanism of Short-Term Synaptic Depression

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King, Richard D., Michael C. Wiest, and P. Read Montague. Extracellular calcium depletion as a mechanism of short-term synaptic depression. J Neurophysiol 85: 1952–1959, 2001. Recent experiments have demonstrated that normal neural activity can cause significant decrements in external calcium levels, and that these decrements mediate a form of short-term synaptic depression. These findings raise the possibility that certain forms of short-term synaptic depression at glutamatergic synapses throughout the mammalian CNS may be influenced by similar changes in external calcium. We use a computational model of the extracellular space, combined with experimental data on calcium consumption, to show that such short-term depression can be accounted for by changes in calcium just outside active synapses, provided that external calcium diffusion is restricted. Remarkably, the model suggests the novel possibility that synapses may possess private pools of external calcium that enforce some forms of short-term depression in a synapse-specific manner.

INTRODUCTION

Extracellular calcium plays a critical role in many neuronal processes, including the regulation and modulation of synaptic release events (Dittman and Regehr 1998; Mintz et al. 1995; Pumain 1998; Tsodyks and Markram 1997). Previous theoretical suggestions (Nicholson 1980) and computer simulation studies of external calcium dynamics, in which external calcium was free to move throughout the complicated interstices of the extracellular space (Eagleton 1998; Egelman and Montague 1998, 1999; Rusakov et al. 1999; Wiest et al. 2000), suggested that fluctuations in the level of extracellular calcium may constitute an information-bearing signal in the brain. The results of these modeling studies suggested in particular that while postsynaptic dendritic spiking activity was likely to decrement significantly local external calcium, electrically active presynaptic boutons were unable to significantly modulate the neighborhood calcium concentration.

The local geometry of brain tissue and the character of the extracellular matrix are unlikely to be as uniform as was assumed in these previous modeling studies. If small volumes of tissue were effectively isolated from the surrounding external calcium “bath,” then presynaptic activity could permit normal neural activity to create fluctuations in the ionic composition within the enclosed spaces that are larger than ionic fluctuations under more open conditions. Given the known modulation of synaptic release by external calcium concentra-

tion, such modulation would contribute to short-term synaptic depression at any local presynaptic terminals.

Gliai ensheathment provides one potential means of functionally isolating local volumes from the surrounding extracellular milieu. Excellent examples of well-defined glial ensheathe-ment of synapses are found in the lateral geniculate nucleus (Wilson 1989), hippocampus (Shepherd and Harris 1998), cerebellum (Rossi and Hamann 1998), and retina (Stone et al. 1995). Calyx-type synapses offer another means to create isolated or quasi-isolated synaptic clefts by enveloping the postsynaptic dendrite locally. Recent experimental measurements of calcium currents at giant calyx-type synapses in chick ciliary ganglion (Stanley 2000) and rat brain stem (Borst and Sakmann 1999) provide strong evidence of calcium depletion in those synaptic clefts. Neither glia nor Calyceal synapses appear in serial electron-microscope reconstruction images to form tight seals around postsynaptic active zones; thus the experimental evidence that calcium depletion does occur (and mediates synaptic depression) in the clefts of Calyx-type synapses suggests that in vivo the seals may be tighter than they appear in electron-microscope reconstructions, or that other impediments to diffusion may cooperate with geometrical enclosures to create quasi-isolated compartments of tissue.

This paper uses a model of calcium diffusion in the extracellular space to show that structures that impede the diffusion-dependent replenishment of calcium in the synaptic cleft do increase the magnitude of calcium fluctuations at synapses, and 2) that modulation of transmission probabilities via extra-
cellular calcium depletion can account for published short-term synaptic depression data from cortical synapses.

METHODS

We model extracellular calcium consumption, diffusion, and replenishment using 1) a finite-difference model and 2) an analytic approximation. The finite-difference model allows direct simulation of the diffusion of extracellular calcium within a local volume of active units along with explicit representation of boundary conditions (such as the degree to which an extracellular volume is isolated from neighboring regions). However, this process is computationally expensive. The analytic approximation is efficient when average behavior, rather than detailed profiles of individual spikes, is desired, and when diffusion is not a major influence, i.e., when local volumes are effectively enclosed.

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**Finite difference model**

The finite difference model of the extracellular space (called ECS) (Engelman and Montague 1998) consists of intracellular and extracellular compartments, each of which holds a vector of state variables (calcium concentration, voltage, channel density, and channel activation parameters). Arranging and combining these compartments together at the appropriate scale permits us to incorporate three-dimensional neural elements such as boutons and dendrites. Diffusion in the finite difference model occurs with an effective diffusion constant of 200 μm²/s between contiguous extracellular compartments (Nicholson and Rice 1987; Wiest et al. 2000). Calcium consumption (through voltage-gated calcium channels) and replenishment (via 1st-order calcium pumps) occur between contiguous extracellular and intracellular compartments.

Three classes of Hodgkin-Huxley (H-H) type calcium channels were used: 1) high-voltage activated, inactivating (N-like channel), 2) high-voltage activated, noninactivating (L-like channel), and 3) low-voltage activated, inactivating (T-like channel). A modified Goldman-Hodgkin-Katz model was used for the calcium current through each channel type $j$.

$\frac{\partial C}{\partial t} = F(C, N) + D \nabla^2 C \tag{1}$

$\frac{\partial N}{\partial t} = G(C, N) \tag{2}$

where $F$ and $G$ are nonlinear functions of $C$ and $N$. $\nabla^2$ is the Laplacian operator that represents the spatial curvature of the external calcium concentration, and $D$ is the effective diffusion coefficient for calcium. We consider the case of a single synapse or small group of synapses with access to a private pool of extracellular calcium; hence we set the $D \nabla^2 C$ term to 0 (no diffusion from neighboring regions). In such an enclosed volume, the total amount of calcium is conserved and must sum to a total value $T$. Thus $(\partial C/\partial t) = -(\partial N/\partial t)$. Linear approximation of Eq. 1 with constant terms set to 0 yields

$\frac{\partial C}{\partial t} = -\alpha C + \beta N \tag{3}$

Equation 4 can be separated and integrated to yield the following solution, where $C(t) = C_0$

$C(t) = \frac{\beta T}{\alpha + \beta} + \frac{C_0(\alpha + \beta) - \beta T}{\alpha + \beta} e^{-(\alpha + \beta)t} \tag{5}$

In the case where $T \approx C_0$, Eq. 5 simplifies to

$C(t) = C_0 \left[ \frac{1}{1 + \alpha \beta} + \frac{1}{1 + \beta \alpha} e^{-(\alpha + \beta)t} \right] \tag{6}$

**Parameters for the analytical model**

The constants $\alpha$ and $\beta$ have a natural relationship to experimentally measured biological parameters. First-order calcium pumps mediate the extrusion of calcium from the inside of the synapse into the extracellular space at a rate proportional to the amount of internal calcium. The constant $\beta$ is therefore inverse of the time constant ($\tau$) of these calcium pumps. Experimentally, the parameter $\tau$ is on the order of 100–500 ms (Philipson and Nicoll 1993; Schatzmann 1989). We estimate $\alpha$ by taking the influx of calcium as proportional to the product of the external calcium level and the rate of action potential invasion. Thus $\alpha = kr$, where $k$ is a dimensionless scaling parameter that characterizes the amount of calcium intake per spike. The value of $k$ is less constrained by experimental data. In *dendrites*, the range of $k$ may be estimated by dividing the experimentally measured values of the number of calcium atoms consumed per spike per square micrometer of membrane (Helmchen et al. 1996) by the total number of calcium ions in the cleft. This leads to a rough range for $k$ from 0.18 to 1.0. Using a value from this range in our model, we can match the steady-state depression data but not the time course as reported by Abbott et al. (1997) (not shown). To account for the spike-by-spike data, we must assume that $k$ is around 0.1 (see Fig. 6). This choice implies that synaptic terminals consume less calcium per square micrometer of membrane than do dendrites, consistent with other observations (Rusakov et al. 1999).

The firing rate $r$ represents a fixed increase from an initial rate $R_s$ to a new rate $R$. In the case where the initial rate $R_s$ is nearly zero, such as in cortical slices, $r$ equals $R$. Substituting these biological constants into Eq. 6 yields

$C(r, t) = C_0 \left[ \frac{1}{1 + \alpha \tau r} - \frac{1}{1 + (\tau r k)} e^{-(\tau r k)x} \right] \tag{7}$

In words, Eq. 7 characterizes the influence of a step change in the firing rate on the time course of external calcium fluctuations. As a final step, Eq. 7 can be divided by the volume of the extracellular space ($V_{\text{extr}}$) to yield the results in terms of concentration.

**RESULTS**

**Enclosure amplifies and prolongs the calcium decrement**

We used a finite-difference model to calculate the expected calcium decrement around two asynchronously active boutons...
over a range of Poisson firing rates under the following boundary conditions: 1) there are no physical barriers to impede diffusion from replenishing the calcium consumed during synaptic activation, or 2) the bouton pair is fully ensheathed, with the only calcium replenishment into the extracellular space coming from first-order calcium pumps. The results are shown in Fig. 1. An enclosure around two boutons amplifies the calcium decrement for any given firing rate, and prolongs the rate of recovery following stimulation (the latter not shown). An analytic solution, which is derived for the enclosed case, is shown as the dashed curves in Fig. 1. The analytic calcium profiles resemble the finite difference model under enclosed conditions (Fig. 1B), suggesting that the analytical approximations are appropriate over a physiological range of firing rates.

FIG. 1. Open vs. closed geometric conditions. Extracellular calcium concentration through time computed by the finite-difference model for a range of firing rates. There are 2 active boutons in the simulation, each firing with an independent Poisson spike train (black line, 50 Hz; gray line, 100 Hz). If multiple boutons cohabit a given enclosure, the possibility arises for conditional interactions among terminals, in addition to the individual short-term depression effect, which is the focus of this study. A: open volume; the 2 boutons are contained within a 7 × 7 × 7 volume (each modeled tissue unit is a cube 0.826 μm on a side) with no enclosures around the pair. B: enclosed volume; same parameters as in A, except that the clefts around 2 boutons are closed off from the outer 7 × 7 × 7 volume. Without the diffusion of calcium from the neighboring volume, the calcium is depleted from the extracellular space within the enclosure. Dotted lines: analytic approximation of the external calcium concentration inside an enclosed volume, using Eq. 7. The analytical model approximates the finite-difference model by assuming 1) continuous calcium consumption instead of discrete consumption events, and 2) each spike consumes independently of every other spike (i.e., there is no refractory period after a spike).

Degrees of enclosure: diffusion in the finite difference model

Given that restricting the diffusion of calcium around boutons amplifies the calcium decrement, how does the degree of enclosure affect the size of the extracellular calcium signal? We can set the degree to which diffusion is limited using partially open geometrical conditions in the finite difference model (Fig. 2). We model increased isolation by scaling the calcium flux between enclosed and open cleft units by γ, which indicates the percentage of diffusion paths that are available. For a completely isolated space, γ = 0, while γ = 1 for the maximally open condition. Within the enclosure, D = 200 μm²/s, which is the effective diffusion constant of calcium in the extracellular space (Nicholson and Rice 1987; Wiest et al. 2000), and γ = 1. As shown in Fig. 2, when γ = 0.01, the calcium transient is amplified but returns quickly to baseline levels. When γ < 0.0005, there is both an amplification of the calcium signal for each spike, as well as a significant drop in the steady-state calcium level around the synapse. As expected, when enclosure has a greater degree (i.e., γ is smaller), the steady-state level of extracellular calcium will drop lower for any given firing rate.

Encoding the rate of activity into the level of extracellular calcium

The fact that every spike causes fluctuations in the extracellular calcium level suggests a novel information-bearing role for calcium: measuring the calcium level in a local region gives a measure of how electrically active that region is (Wiest et al. 2000). The relationship between the steady-state calcium level (C_{ss}) and the rate, as taken from Fig. 1, A and B, is shown in Fig. 3. We can see that there is a region in the plot in which the...
level of extracellular calcium is a linear function of the change in firing rate plotted on a logarithmic scale.

\[ C_{ss}(r) = -\eta \log (r/R_o) + C_{ss}(R_o) \] (8)

or

\[ c_{ss}(r) = -\eta \log (r/R_o) + \epsilon \] (9)

where \( c_{ss}(r) = C_{ss}(R) - C_{ss}(R_o) \) and \( \epsilon = C_{ss}(R_o) - C_{ss}(R_c) \) represents the lowest frequency for which the linear relation holds (\(-10\) Hz; see Fig. 3); \( r \) must be positive (i.e., \( R > R_o \)) and greater than \( R_o \) for the log relationship to be valid. The time it takes to reach this regime depends on the rate of firing (i.e., with faster firing rates, it takes less time to reach the linear regime). We estimate that it takes from 5 to 10 spikes before the calcium depletion is in the linear regime, based on the time needed to reach steady state in Fig. 1. Note that the log relationship holds in both the open and enclosed conditions, with the enclosure changing the slope from \( \eta = 0.08 \) to \( \eta = 0.26 \). However, in the open case, the change in the external calcium concentration is probably too small to be detected, based on previous estimates of the minimum detectable fluctuation (Egelman and Montague 1999; Wiest et al. 2000).

One consequence of the log relation is that doubling any rate (as long as the rate is still in the linear regime) in a volume will always create the same size fluctuation in calcium level (i.e., changing from 10 to 20 Hz will create the same size signal as changing from 40 to 80 Hz).

External calcium and synaptic transmission probabilities

The probability of a synapse transmission given an action potential \( (P_T) \) has been measured using optical techniques (Mintz et al. 1995; Qian et al. 1997); see Fig. 4. Our analysis of this data shows synaptic transmission probability to be proportional to the square of the extracellular calcium level

\[ P_T = \nu [Ca^{2+}]^2 \] (10)

where \( \nu = 0.24 \) mM\(^{-2}\). Thus fluctuations in the level of calcium would amount to changes in the square root of synaptic transmission probability. Substituting in the analytical approximation for the external calcium level as a function of an increase in firing rate \( (r) \) in an enclosed volume (Eq. 7, see Fig. 3),

\[ \text{FIG. 3. Logarithmic relation between firing rate and extracellular calcium.} \]

\[ \text{FIG. 4. Relationship between external calcium and postsynaptic response.} \]

\[ A: \text{Presynaptic Calcium Influx} \]

\[ B: \text{Postsynaptic Response} \]
A range of values for $t$

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We used the relationships shown in Fig. 5 to compare the predictions of the model to the experimental results of Tsodyks and Markram (Fig. 6A) and Abbott et al. (Fig. 6, B–D). The proposed mechanism matches the data at low and high frequencies. With one further assumption about the scaling of the $\kappa$ consumption parameter (Fig. 6A, legend), the model also provides a quantitative match to the dependence of synaptic depression on external calcium levels as reported by Tsodyks and Markram (Fig. 6A). The time course of recovery from depression, as described by Eq. 7, depends on the rate constant of the calcium pumps (Schatzmann 1989) ($\tau$), which places it well within the range of recovery times reported in other studies (Abbott et al. 1997; Dittman and Regehr 1998; Tsodyks and Markram 1997). It should be noted that and $\tau$ and $\kappa$ are parameters whose range was estimated from independent experiments unrelated to assessments of synaptic depression (see METHODS).

The depletion of calcium from the extracellular space also places a constraint on density of synaptic transmissions per unit time per unit tissue volume. The average number of transmissions that occur per second is equal to the number of spikes that occur per second (rate) times the probability of transmission per spike ($P_T$). As shown in Fig. 7, the probability of transmission ($P_T$) is approximately equal to the inverse of the firing rate times a constant ($\chi$) at rates of $r > \sim 40$ Hz. Therefore

$$\frac{\text{number of transmissions}}{\text{second}} = rP_T = rx(\text{Ca})^2 = \frac{r}{\chi(1/r)} = \chi$$

In this view, calcium acts as a normalizing fluid that sets the total number of transmissions in an enclosed volume to a constant level. Such an arrangement would enable the tissue to register changes in slow firing inputs as well as rapidly firing inputs (Abbott et al. 1997).
particular, we scale the value of that the relative depression is greater when the calcium concentration is higher, which is consistent with Varela et al. (1997). In capture the influence of initial external calcium concentration on the steady-state amplitude of the postsynaptic current, and the fact

DISCUSSION

Our simulations show that barriers to calcium diffusion in the extracellular space of brain tissue could modulate changes in external calcium during neural activity, suggesting that isolated calcium pools around synapses could be used computationally. We also found that spike activity in an enclosed tissue volume is integrated and encoded logarithmically in the external calcium level. This measure of average local activity is thus available for further processing by neurons or glial cells (Verkhratsky and Kettenmann 1996). For example, the logarithmic dependence of the extracellular field potentials after activation across a range of firing rates with 15 spikes. The solid line (same solid line as in Fig. 5, A and B, right) shows the prediction of the analytical model (Eq. 11; \(C' = 1.6 \text{mM}, \kappa = 0.11, \tau = 300 \text{ms}, \eta = 2\); middle trace; \(C' = 2 \text{mM}, \kappa = 0.14, \tau = 300 \text{ms}, \eta = 2\); bottom trace; \(C' = 1.5 \text{mM}, \kappa = 0.105, \tau = 300 \text{ms}, \eta = 2\)).: the change in release probability \((\Delta P)\) due to instantaneous rate changes from \(r\) to \(r + \Delta r\) for 2 different values of the ratio \(\Delta r/r\). The changes are of constant magnitude for constant ratios of \(\Delta r/r\). For example, the response due to a rate change from 10 to 20 Hz is the same magnitude as the response from 20 to 40 Hz. Consequently, changing the rate by a constant amount will produce successively smaller increases in response. Dotted line: changes in rate by a factor \(\Delta r/r = 1\); solid line: changes in rate by a factor \(\Delta r/r = 0.5\). Parameter settings are the same as in B.

Synaptic depression: comparing extracellular calcium to other mechanisms

Our results demonstrate the biophysical plausibility of external calcium depletion as a mechanism of short-term synaptic depression; however, they do not exclude mechanisms internal to the synapse, such as the depletion of vesicle pools, which are believed to be involved in synaptic depression (Castro-Alamancos and Connors 1997; Dobrunz and Stevens 1997;
Our results raise the question of the nature of the hypothesized barriers to diffusion in the extracellular space. Glial investments around synapses could create a compartment in which local external calcium fluctuates rapidly due to spike activity, yet equilibrates on a slower time scale with the surrounding regions of the extracellular space. Other factors, such as extracellular matrix molecules, could contribute to slowing diffusion or to holding glia in place. For a fixed rate of calcium extrusion, changes in the private external volume available to each synapse could provide sensitive control over the effective local levels of external calcium. Consequently, local structural modulation could act to modulate those parts of short-term depression controlled by changes in external calcium levels (Fields et al. 1987; Hosokawa et al. 1997). Complex calcium signaling pathways between glial cells and neurons support such an interpretation (Verkhratsky and Kettenmann 1996). While our model cannot predict the relative importance of various possible barriers to diffusion around particular synapses, the current results suggest one novel computational role for glia in segregating (different compartments) and integrating (within a compartment) information coded in the external calcium level.

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