Presynaptic calcium dynamics of learning neurons

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Abstract: We present a new model for the dynamics of the presynaptic intracellular calcium concentration in neurons evoked by various stimulation protocols. The aim of the model is twofold: We want to discuss the calcium transients during and after specific stimulation protocols as they are used to induce long-term-depression and long-term-potentiation. In addition we would like to provide a general tool which allows the comparison of different calcium experiments. This may help to draw conclusions on a wider base in future.

Introduction

A most fascinating challenge in neuron biology is a deep understanding of the mechanisms involved in long-term-effects (LTE) such as long-term-potentiation (LTP) and long-term-depression (LTD). The multiplicity of possibly important mechanisms is immense and is explored in a great variety of experiments. However, the interpretations of those experiments are not as conclusive as they could be if it was possible to better compare experiments executed on different systems. We claim that a lot of detailed information on LTE is hidden in presently available experiments.

One possible way to uncover this hidden knowledge is to construct a tool which is able to translate different experiments into a common language and then to compare them quantitatively. Such a tool is provided here for the analysis of the intracellular calcium concentration in presynaptic nerve terminals. It is very well established by experiments that LTE are mostly connected with dynamical changes in the calcium concentration which, therefore, is an appropriate observable to study the origin of effects as LTD and LTP. Already on this very early level of LTE-induction a comparative quantitative evaluation of different experiments may lead to new insights. The experiments have been done using different systems or using the same system under different conditions. In addition, a dependence of the presynaptic calcium dynamics on the corresponding target cell has been observed. In order to compare those experiments quantitatively one has to determine characteristics of the experiment that are important for the calcium dynamics and to introduce them into the model terminology.

In the following we will develop a corresponding model which can be used for comparison of presynaptic calcium dynamics in different experiments. The model
has to be adjusted to specific experiments in a well-defined procedure, which is illustrated for the example of presynaptic nerve terminals in the rat neocortex \[2\]. The results found here are discussed in the context of LTE. For more details of the model and the results presented here we refer to \[3\].

The model on the level of single proteins

We construct a new deterministic one-compartment model for the presynaptic calcium dynamics. It is formulated in terms of a set of coupled differential equations for the intracellular calcium concentration \(c\):

\[
\frac{\partial c}{\partial t} = \frac{G \rho_{U} J_{U} \left(g_{U}(U), U(t), \bar{U}(c)\right) - \rho_{P} J_{P}(g_{P}(c)) - \rho_{E} J_{E}(g_{E}(c)) + L}{1 + \Theta_{b}(c) + \Theta_{i}(c)}
\]

where \(\rho_{U,P,E}\) are the surface densities of the voltage-gated channels (HVA), the PMCA-type calcium pumps, and the natrium-calcium exchange (type 1), respectively. \(J_{U,P,E}\) are the corresponding single protein currents, and \(g_{U,P,E}\) the single protein open probabilities. \(G\) is a geometry factor (ratio of surface and volume in the compartment), \(z\) is the valence of the calcium ions, \(F\) the Faraday constant, \(\bar{U}(c)\) the calcium dependent calcium reversal potential, and \(L\) the leak current which is determined by the steady state condition. The open probabilities \(g_{P,E}\) follow a standard Hill equation in the case of the pumps and the exchangers \[4, 5\] while the open probability for the voltage gated calcium channels obeys \[6\]

\[
\frac{\partial g_{U}(U)}{\partial t} = \frac{1}{\tau} \left\{ \left[ 1 + \exp \left\{ \frac{U_{1/2} - U}{\kappa} \right\} \right]^{-1} - g_{U}(U) \right\} , \quad (2)
\]

with \(\tau\) the channel mean open time, \(U_{1/2}\) the half activation voltage, and \(\kappa\) the steepness factor. The buffers (endogenous and indicator) are treated in a quasi-steady state approximation, which claims that the calcium binds and dissociates faster than the typical time scale under consideration. Then the dynamical behavior of the buffers reduces to a correction factor in Eq. (1) which depends on the calcium concentration only:

\[
\Theta_{b}(c) = \frac{b_{\text{max}} K_{b}}{(K_{b} + c)^{2}} \quad \text{and} \quad \Theta_{i}(c) = \frac{i_{\text{max}} K_{i}}{(K_{i} + c)^{2}} . \quad (3)
\]

Here \(b_{\text{max}}\) and \(i_{\text{max}}\) are the total concentrations of the endogenous buffer and the indicator, respectively. \(K_{b,i}\) are the corresponding dissociation constants.

The differential equations are solved numerically and the solution describes the time course of the calcium concentration resulting in response to single action potentials or to series of action potentials (as they are used to induce LTD or LTP). The above mentioned aspired generality of the model is reflected in a separation of the model parameters into three classes, described in the following subsections.
Universality

The model is universal enough to be applicable to a wide class of different neuron types. To this end the model is based on the experimental knowledge about single proteins which are postulated to have neuron-type independent properties. These are the single protein characteristics $g_x$ (including all derived physiological properties) and the single protein transmembrane currents $J_x$, where $x$ stands for the corresponding type of protein (see e.g. [4, 5, 6]).

Type specificity

The model is specific enough to be applicable to well defined neuron types. This is achieved by the introduction of measurable neuron-type specific parameters which has to be determined for each experiment separately. Basically, these are the protein densities $\rho_x$ in the membrane. As no space resolution of the calcium concentration is considered, these densities may be thought as average values over the whole synaptic membrane. Also the concentration of the endogenous buffer $b_{\max}$ and its dissociation constant $K_b$ belong to the neuron-type specific class of parameters. Finally, the surface to volume ratio $G$ of the synaptic compartment quantitatively determine the concentration changes due to transmembrane currents.

Condition specificity

The model includes enough general specifications in order to adjust the model to specific experimental conditions. The form and amplitude of the action potential $U(t)$ is simulated with a system of coupled differential equations (not shown here). The LTE-stimulation protocols used in experiment are simulated with a corresponding series of single action potentials. Intracellular calcium concentrations are generally visualized with the help of calcium indicators. They act as an additional buffer in the cell and, therefore, may influence the calcium dynamics. In the model they are treated in complete analogy to the endogenous buffer and are characterized by the indicator specific dissociation constant $K_i$ and the used indicator concentration $i_{\max}$.

Adjustment to a specific experiment

The idea of this semi-universal model for presynaptic calcium dynamics is to determine the universal parameters using single protein experimental data and to maintain the resulting values for the evaluation of different systems and experimental conditions. Universality has to be understood as the postulated statement, that universal parameters are not the parameters that are most sensitive to a transfer from one experiment to another. The adjustment of the model to a
specific experiment is achieved through the determination of the system-specific and condition-specific parameters. Note, that without any exception these are parameters with direct physiological interpretation. Therefore, most of them may be accessible up to a sufficient precision in several experiments.

In the described procedure the main part of the model is determined by sources that are independent of the experiment under consideration. Therefore, the value of the model is tested by its capability of reproducing the answer of the calcium concentration to single action potentials on the basis of those independent and fixed universal parameters. As in general not all specific parameters will have been determined in the experiment under consideration, we will fit the remaining unknown parameters to the single action potential calcium response. With the help of a thus defined model it should be possible to analyse the measured calcium transients evoked by LTD or LTP stimulation protocols.

This has been executed for an experiment on single nerve terminals of pyramidal neurons in the neocortex of rats [2]. Most specific parameters used in the model are directly accessible in this experiment. This concerns for example the form of the action potential applied to the nerve terminal, the geometry (i.e. the surface to volume ratio), the concentration of endogenous buffer, and the characteristics and concentrations of the used calcium indicator (magnesium green). Therefore, we are in the situation that the whole model is a priori determined either by independent sources (concerning universal parameters) or by the available data from the experiment under consideration. The only unknown parameters are the surface densities of the calcium transport proteins. These are fitted to the measured calcium transient evoked by single action potentials. The result Fig. 1 shows, that the measured calcium transient is reproduced correctly.

**LTE stimulation**

In order to check if the thus defined model has predictive power, we calculate the intracellular calcium transients evoked by series of action potentials with varying frequency. Basically, the model parameters remain unchanged. As in the corresponding experimental setup (see [2] Fig. 9) a different action potential (compared to Fig. 1) has been used, the action potential is adapted in the model and the channel densities are fitted to the single action potential calcium response, correspondingly. In addition the indicator concentration is enhanced, which is considerably higher in this experimental setup. Now the 10 Hz stimulus is applied and the result is shown in Fig. 2. The model result is in quantitative agreement with the calcium transients seen in the experiment: The intracellular calcium concentration reaches a new baseline level during the stimulation process which breaks down when the stimulus is switched off. The calcium concentration oscillates on the top of the new baseline in coherence with the stimulation potential. The amplitude of those oscillations is slightly overestimated by the model.
Figure 1: The calcium transients evoked by single action potentials in single boutons of pyramidal neurons in the rat neocortex (100µM magnesium green). The dotted line shows the best single exponential fit to the experimental values [2], and the full line shows the model result with fitted protein densities.

On this basis we can calculate the calcium transients in response to stimulation protocols with various frequencies. We find that the calcium transients do not overlap for low frequencies typical for LTD-induction. The emergence of a new baseline in the calcium concentration at frequencies around 10 Hz may be interpreted as threshold for the induction of LTP. Note, that this threshold frequency strongly depends on the used calcium indicator concentration. This is especially relevant for the interpretation of experimental results. A stimulation with frequencies around 50 Hz (typical for the induction of LTP) leads to a more pronounced enhancement of the calcium baseline. This qualitative behavior is in agreement with experiments carried out on dendritic spines of pyramidal neurons [7].

Conclusion

Our new model for transients of the presynaptic intracellular calcium concentration evoked by various stimulation protocols reproduces the general behavior observed in experiment. It is exclusively constructed with parameters that have a direct physiological interpretation. Its basis are the single proteins properties. The characteristics of single proteins are considered to be universal in the sense
Figure 2: The calcium transients evoked by a 10Hz stimulus in single boutons of pyramidal neurons in the rat neocortex (500µM magnesium green). The full line represents the model result and the triangles represent the corresponding measured transients [2] (the peak and baseline values, respectively). The dashed line represents the best single exponential fit to the experimental baseline values [2].

that they remain unchanged for different experimental setups. The model has been adjusted to a specific experiment that measured intracellular calcium transients in nerve terminals of pyramidal neurons of the rat neocortex. To this end the parameters specific for this experiment have been extracted from it or, if not available, have been fitted to the single action potential calcium response. The model results turned out to be in quantitative agreement with the experiment, so that we conclude that the model correctly describes the presynaptic calcium dynamics. We did not find any reason for the involvement of calcium-induced-calcium-release in the induction of LTE. However, it seems that an additional mechanism (e.g. calcium channel inactivation) may be necessary to understand the induction of LTD on the level calcium transients.

More generally, the separation of universal and specific parameters enables us to analyse different results observed in several experiments. With the help of our new model one may decide, if those differences are significant or due to different experimental setups.
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