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The importance of stochastic signaling processes in the induction of long-term synaptic plasticity

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ABSTRACT

A stochastic model of the signaling network responsible for the induction of long-term depression (LTD) at the parallel fiber to Purkinje cell synapse is described. The model includes a PKC-ERK-cPLA$_2$ positive feedback loop and mechanisms of AMPA receptor trafficking. It was tuned to replicate calcium uncaging experiments that cause LTD. The ultrasensitive activation of ERK makes the signaling network activity bistable, causing either LTD or not. Therefore, in single synapses only two discrete stable states (LTD and non-LTD) can be expressed. The stochastic properties of the signaling network causes threshold dithering and probabilistic expression of LTD, which allows at the macroscopic level for many different and stable mean magnitudes of depression. When the volume of a single spine is simulated no thresholds for the calcium input signal are present. Such thresholds appear only when the volume of simulation is increased by a factor 100 or more and the model output is then bistable. Similarly, deterministic solutions of the same model show only bistable behavior. LTD induction requires activation of the PKC-ERK-cPLA$_2$ positive feedback loop but this activity is not constant: the activities of ERK and of cPLA$_2$ fluctuate strongly. This is much less the case for PKC which is more constantly activated and thereby promotes a stable output of the pathway.

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1. Introduction

Long-term forms of synaptic plasticity play an important role in most forms of learning (Feldman, 2009). Many processes involved in any form of synaptic transmission and plasticity are known to be stochastic, including neurotransmitter release, opening and closing of ionic channels, receptors and second messengers diffusion, activation and interaction of signaling molecules (Ribrault, Sekimoto, & Triller, 2011). Nevertheless, stochastic aspects of synaptic function are ignored in most models of synapses and of their plasticity (Roth & van Rossum, 2009) or of the signaling pathways involved (Kotaleski & Blackwell, 2010). The few studies where stochastic effects were included in models of induction of cerebellar long-term depression (LTD) (Tanaka et al., 2007) or of long-term potentiation (LTP) in pyramidal neurons (Graupner & Brunel, 2007) assumed that the calcium signal triggering the induction of plasticity was the main source of noise.

In this review paper we examine the stochastic properties of the signaling pathways that cause cerebellar LTD (Ito, 2001, 2002). This form of plasticity is expressed at parallel fiber synapses onto spines on the Purkinje cell. The volume of these spines is about 0.12 μm^3 (Harris & Stevens, 1988) and the number of molecules of any species in such a tiny volume is very small. For example, at rest only few ions of calcium will be present in a spine. Therefore the reaction involving calcium are expected to be very stochastic and, as we will see, the same applies for all components of the signaling pathways involved in cerebellar LTD. This stochasticity has functional consequences. For example, when LTD is induced using the 'physiological' co-activation of climbing fiber and parallel fiber inputs, the amount of LTD induced varies tremendously (e.g. 5%–40%; Coesmans, Weber, De Zeeuw, & Hansel, 2004) and sometimes even fails completely (De Schutter, 1995). Considering that the LTD measured in typical electrophysiological experiments reflects the mean changes at hundreds of parallel fiber synapses, this suggests a strong variability of LTD expression at the level of single synapses.

In this modeling study we focused mostly on simulating a simpler protocol, the LTD induced by a rise of calcium concentration, because the properties of this system have been quantified in great detail experimentally (Tanaka et al., 2007) and allow for a systematic analysis.

2. Model

2.1. Positive feedback loop

Most forms of long-term synaptic plasticity are initiated by a short duration calcium signal in the spine which activates a

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number of signaling pathways, leading to a much slower change in the postsynaptic number of AMPA receptors (AMPAR) (Feldman, 2009; Ito, 2002). In cerebellar LTD it was demonstrated with calcium uncaging methods that a 0.5 s rise of the calcium concentration is sufficient to induce LTD, which then takes 10–20 min to reach its maximum level of depression (Fig. 1(B)) (Tanaka et al., 2007). Bhalla and co-authors proposed that this mismatch in the duration of the input signal and the expression of synaptic plasticity can be explained by a positive feedback loop that is activated by the calcium signal, specifically the activation of a mitogen-activated protein kinase (MAPK) pathway based feedback loop (Bhalla & Iyengar, 1999; Bhalla, Ram, & Iyengar, 2002). The essential components of the corresponding feedback loop in cerebellar LTD are shown in Fig. 1(A). The calcium signal activates two enzymes: Ca^{2+}-dependent protein kinase Cα (PKC) (Newton, 2001) and cytosolic phospholipase A2 (cPLA$_2$) (Burke & Dennis, 2008). PKC phosphorylates AMPAR (Matsuda, Mikawa, & Hirai, 1999) which leads to their removal from the postsynaptic density (see Section 2.2) and the expression of LTD. But PKC also activates the MAPK feedback loop. Fig. 1(A) shows a highly simplified version of this feedback loop with many intermediary reactions removed for clarity. In Purkinje cells the relevant member of the MAPK family of enzymes involved with induction of LTD is called the extracellular signal-regulated kinase (ERK) (Ito-Ishida, Kakegawa, & Yuzaki, 2006). So PKC indirectly activates ERK, which in turn activates cPLA$_2$. cPLA$_2$ completes the feedback loop by producing arachidonic acid (AA), an activator of PKC. The PKC-ERK-cPLA$_2$ feedback loop has been extensively investigated in Purkinje cells, confirming its essential involvement in the initial induction of cerebellar LTD (Tanaka & Augustine, 2008). A detailed description of the PKC–ERK–cPLA$_2$ feedback loop in the model can be found in Antunes and De Schutter (2012).

Based on an earlier model of the MAPK feedback loop in hippocampal LTP (Bhalla & Iyengar, 1999), Kuroda, Schweighofer, and Kawato (2001) developed a model of cerebellar LTD that formed the basis of this study (Antunes & De Schutter, 2012). The new model was extensively updated and expanded to match more recent experimental data (Antunes & De Schutter, 2012).

2.2. AMPA receptor trafficking

The model explicitly simulates the trafficking of AMPAR that was not included in previous models (Bhalla & Iyengar, 1999; Kuroda et al., 2001). This allows to quantitatively match the model output with the experimental data that is expressed as a change of the AMPAR mediated synaptic current (Fig. 1(B)–(C)) (Antunes & De Schutter, 2012; Tanaka et al., 2007).

The phosphorylation of AMPAR by PKC leads to a reduction of their affinity for the glutamate receptor interacting protein (GRIP) in the postsynaptic density (Dong et al., 1997). This results in the unbinding of some of the phosphorylated AMPARs from GRIP and their diffusion out of the postsynaptic density into the spine and on into the dendritic shaft, where they are endocytosed (Wang & Linden, 2000). The model output is the change in the number of synaptic AMPAR, notice that this never drops to zero because a large fraction of AMPAR remains bound to GRIP.

2.3. Model implementation

The model is a large kinetic model of the signaling and trafficking network involved in the induction of cerebellar LTD. It contains 17 proteins plus calcium and AA in the volume of a Purkinje cell spine (Harris & Stevens, 1988) and simulates a total of 207 different reactions. Because of the small volume of spines the number of protein molecules simulated varies from 5 (for Raf, involved in activation of ERK) to 120 (for AMPAR). A complete description of
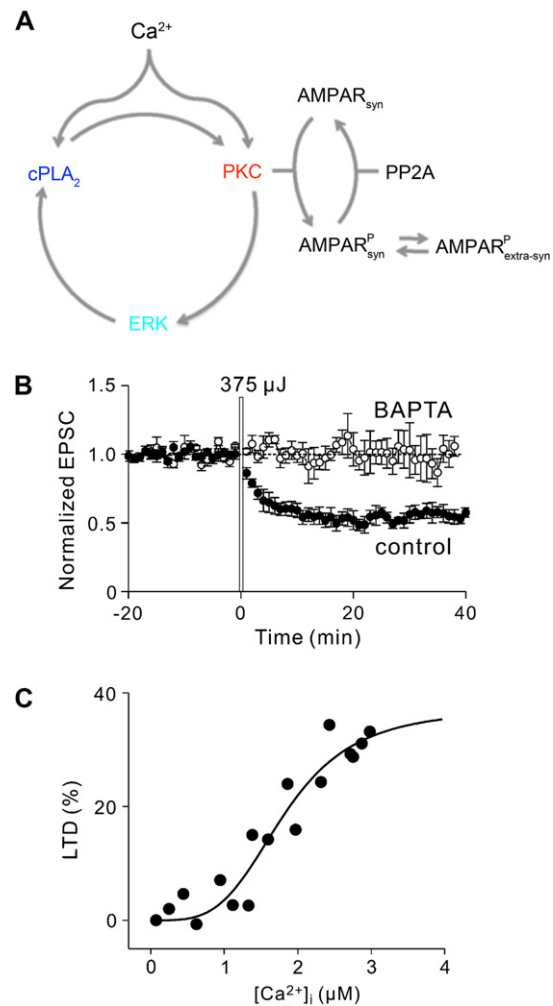

Fig. 1. Simplified block diagram of the model and experimental data. A. The model consists of a signaling network activated by Ca^{2+} and containing a positive feedback loop fundamental for LTD occurrence that is formed by PKC, ERK and cPLA$_2$. PKC is responsible for the phosphorylation of AMPARs, triggering their removal from the postsynaptic membrane. PKC action on AMPARs can be reverted by the protein phosphatase 2A (PP2A). B. Example of LTD induced by photo-activated uncaging of Ca^{2+}, which is blocked by the calcium chelator BAPTA. C. Experimental relationship between the peak amplitude of a 1 s Ca^{2+} signal and the amount of LTD induced, fitted with a Hill function. For Ca^{2+} signals with a longer duration this curve shifts to the left and becomes steeper.
Source: A complete diagram of the model can be found in Antunes and De Schutter (2012). Fig. 1(B) and (C) reproduced with permission from Tanaka et al. (2007), where more details can be found.

all elements of the model was published previously (Antunes & De Schutter, 2012).

Many of the reaction parameters could be obtained from the literature (Antunes & De Schutter, 2012), but about one third of the parameters were not exactly known and had to be searched. The stochastic model was tuned to replicate in detail the quantitative relation between calcium inputs of different amplitudes and durations and the amount of induced LTD that was obtained in calcium uncaging experiments (Fig. 1(C)) (Tanaka et al., 2007). Matching these quantitative measurements, which are unique in the synaptic plasticity literature, together with the requirement that no spontaneous LTD occurs in the absence of calcium influx, imposed strong constraints on the stochastic model.

The AMPAR trafficking was implemented as a four compartmental model with diffusion simulated as a first order reaction (Antunes & De Schutter, 2012; Earnshaw & Bressloff, 2008).

A more complex model was constructed to simulate induction of LTD by co-activation of climbing and parallel fibers. This