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Mechanisms producing time course of cerebellar long-term depression

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ABSTRACT

Cerebellar long-term depression (LTD) is induced by short-lasting synaptic activities, progressively expressed, and then maintained for hours or longer. Short-lasting events, such as calcium transients, are activated and required for the induction of LTD. Further, a positive-feedback kinase loop was shown to follow the transient events and to aid the transition between LTD induction and prolonged synaptic depression. Yet, it is not entirely clear as to how LTD is maintained and how the maintenance mechanisms are activated, mainly because of a lack of experimental studies regarding this topic, while an idea has been theoretically proposed. A new analysis of the experimental results suggests that early maintenance mechanisms display a threshold behavior and that they may be of stochastic nature. This suggestion is conceptually consistent with an idea from a computational study, which postulates that other bistable switch systems are required for LTD maintenance. We thus propose that cellular mechanisms showing a threshold behavior and a stochastic nature maintain LTD, and that future experimental studies in search of such mechanisms would be an important step toward fully understanding the time course of LTD.

1. Introduction

It has been known that synapses between cerebellar Purkinje cells and parallel fibers (PFs) undergo long-term depression (LTD). This occurs as two excitatory inputs onto Purkinje cells, the PFs and the climbing fiber (CF), are simultaneously and repeatedly activated (Fig. 1(A)). Although the precise functions of such cerebellar LTD are still under debate, it seems to have an impact on the function of cerebellar neural networks; the pause of simple spikes in Purkinje cells, which is seen after burst stimulation of PFs, is modified by the induction of LTD (Steuber et al., 2007). Therefore, LTD is a mechanism for inducing prolonged changes in cerebellar neural network activity. Identifying the signaling mechanisms involved in LTD induction and maintenance is therefore critical to understanding cerebellar function.

Similar to other forms of long-term synaptic plasticity, cerebellar LTD is induced by a few minutes of synaptic activity, yet lasts for hours or longer. Intracellular signaling molecules are already active during the short-lasting synaptic activities and many molecules have been linked to the induction of LTD (Ito, 2001). In contrast, the events that occur after the induction of LTD to produce persistent synaptic depression are not well understood. While computational studies have proposed models of these events (Kawato, Kuroda, & Schweighofer, 2011; Kuroda, Schweighofer, & Kawato, 2001; Ogasawara & Kawato, 2009), experimental evidence to support or argue with such models are lacking. Nevertheless, a couple of experimental studies demonstrated a process working in the expression phase, which is a phase right after the induction (Le et al., 2010; Tanaka & Augustine, 2008). Moreover, a new analysis of the experimental results suggests features of an event following the expression. Here we summarize experimental results that provide information toward understanding the mechanisms producing the time course of LTD, and discuss what we know and what we have yet to learn.

2. Time course of LTD

Cerebellar LTD can be divided into three temporal phases, induction, expression, and maintenance (Fig. 1(B)). Neuronal stimulation equivalent to simultaneous activity in the PFs and the CF initiates LTD. This period of triggering LTD can be defined as the induction phase. The expression phase is a period when depression is in process. The time course of expression seems to vary according to stimulus conditions or preparations (Ito, 2001). For example, slow and gradual expression, which lasts for 20–60 min, can be observed when 1 Hz of PF stimulation is paired with CF stimulation or Purkinje cell depolarization in cerebellar slice preparations (e.g. Tanaka & Augustine, 2008). On the other hand, a more rapid expression that occurs within a few minutes can be observed in other experiments using slice preparations or in cultured Purkinje cells. Although it is not known as to what determines the time course of LTD expression, it may depend on how effectively the stimuli can activate intracellular signaling molecules responsible for the expression of LTD. Once depression reaches a maximum level, the depressed level is maintained for a few hours or longer.

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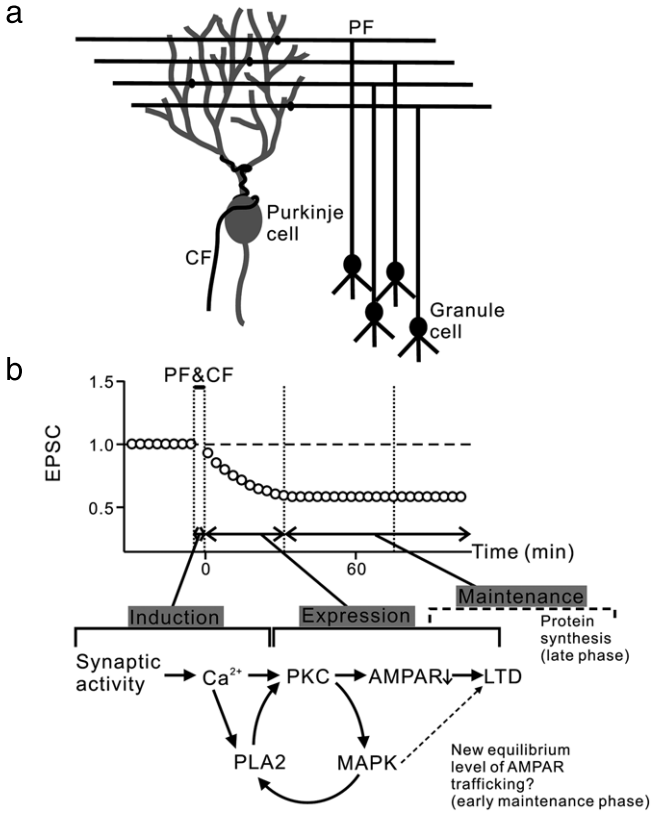

Fig. 1. (A) Schematic drawing of the two excitatory inputs onto a Purkinje cell, namely parallel fibers (PF) and a climbing fiber (CF). (B) Summary of simplified and prospective mechanisms producing the time course of LTD. See text for abbreviations.

The maintenance phase is sometimes divided into early and late phases (see below). It is not known whether the depression is terminated after a certain period.

3. Mechanisms of LTD expression

Previous studies have discovered many signaling molecules involved in LTD induction. Specifically, an increase in intracellular calcium (Ca^{2+}) concentration is necessary and could explain several features of LTD induction (Fig. 1(B)) (Finch, Tanaka, & Augustine, 2012). Furthermore, the expression of LTD correlates with a reduction in the number of synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). AMPARs are phosphorylated by protein kinase C (PKC) and the phosphorylated AMPARs are actively internalized via endocytosis during the LTD expression phase (Steinberg et al., 2006). A Ca^{2+} sensitive isoform of PKC, PKCα, is responsible for LTD expression (Leitges, Kovac, Plomann, & Linden, 2004) and LTD expression could thus be mediated by Ca^{2+}-dependent PKC activation. However, because the increase in Ca^{2+} concentration is transient and short-lasting, Ca^{2+}-dependent PKC activation is an unlikely candidate underlying the prolonged expression of LTD. A computational model proposed that a positive feedback loop, which includes activation of PKC and mitogen-activated protein kinase (MAPK), could bridge the temporal gap by sustaining the activities of these kinases (Kuroda et al., 2001). This loop was indeed tested experimentally and was demonstrated to be responsible for prolonged expression of LTD (Fig. 1(B)) (Tanaka & Augustine, 2008). Another experimental study also supports the idea that the positive feedback loop is responsible for LTD expression, as it demonstrated that other molecules, such as cyclooxygenase-2 and prostaglandin D_2 or E_2, seem to work in this loop around the period of LTD expression (Le et al., 2010).

4. Mechanisms of LTD maintenance

The next question is how a depressed level of synaptic activity can be maintained. Several experimental studies using cultured Purkinje cells have indicated requirements for transcriptional and translational cellular events in the late phase of LTD, which is defined as a phase beginning 60 min after induction. Activity-driven transcriptional regulators, namely the cAMP-responsive element binding protein and the Ca^{2+}/calmodulin-dependent protein kinase type IV, were implicated in this phase (Ahn, Ginty, & Linden, 1999), but it is not clear as to which transcripts are regulated by these transcriptional regulators. Recently, another transcriptional regulator, serum response factor (SRF), was implicated in the late phase of LTD: SRF binding to the SRE 6.9 site in the promoter region of the synaptic protein Arc, and subsequent SRF-dependent Arc expression, were found to be required for the late phase of LTD (Smith-Hicks et al., 2010). Further, a requirement for persistent dynamin-mediated endocytosis, which may also depend on Arc expression, was reported (Linden, 2012).

These studies using cultured Purkinje cells have advanced our understanding of the maintenance mechanisms of LTD. However, there are still some questions to be addressed. The first question is whether the abovementioned signaling molecules are also involved in late-phase LTD in slice preparations or *in vivo*. In fact, it is not clear as to whether or when newly synthesized protein-dependent late-phase LTD is initiated in slice preparations, because bath application of translational inhibitors blocks its induction (Karachot, Shirai, Vigot, Yamamori, & Ito, 2001).

Assuming that similar mechanisms as observed in cultured Purkinje neurons account for the maintenance of the late phase of LTD in intact cerebellar networks, there are still at least two important questions to be answered: (a) how early maintenance between the expression phase and late phase is achieved, and (b) how transitions between these phases are made. Although these questions have not yet been directly addressed, there is a clue in the reanalyzed data of previous results. As mentioned above, the PKC–MAPK positive feedback loop is responsible for prolonged expression of LTD, which takes place 20–30 min after induction (Tanaka & Augustine, 2008). This conclusion arose after timed application of a PKC inhibitor; when the inhibitor was applied at 20 min or less after LTD induction, LTD was blocked or reduced. However, if the inhibitor was applied at 30 min or later, it had little or no effect on LTD. Fig. 2(A) shows the averaged time course of LTD in the absence or presence of a PKC inhibitor, which was applied at 10 or 20 min after LTD induction (Tanaka & Augustine, 2008). In order to clarify the effects of this inhibitor, we further looked into these results by calculating the levels of LTD before and after application of the inhibitor, and by plotting individual data (closed symbols) together with averaged data (open symbols, Fig. 2(B) and (C)). While LTD progressively developed around 10 min after the induction in control (gray triangles in Fig. 2(B)), LTD was blocked by the PKC inhibitor applied at 10 min (red circles in Fig. 2(B)). This blockade of LTD was observed in all 5 cells. When this inhibitor was applied at 20 min (Fig. 2(C)), LTD was slightly reduced on average (green inverted triangles). However, there seemed to be two different responses to PKC inhibition. In one group (4 out of 6 cells; blue squares in Fig. 2(C)), the process of LTD was similar to control (gray triangles in Fig. 2(C)). In contrast, in 2 out of 6 cells, LTD was blocked and EPSC amplitude returned toward the basal level (red circles in Fig. 2(C)). Similar results were also obtained when an inhibitor of phospholipase A2 (PLA2), which is another component of the positive feedback loop, was used: while LTD was blocked when the PLA2 inhibitor was applied at 10 min after the induction (Fig. 2(D)), there were two different responses to the PLA2 inhibitor applied at 20 min (Fig. 2(E)).