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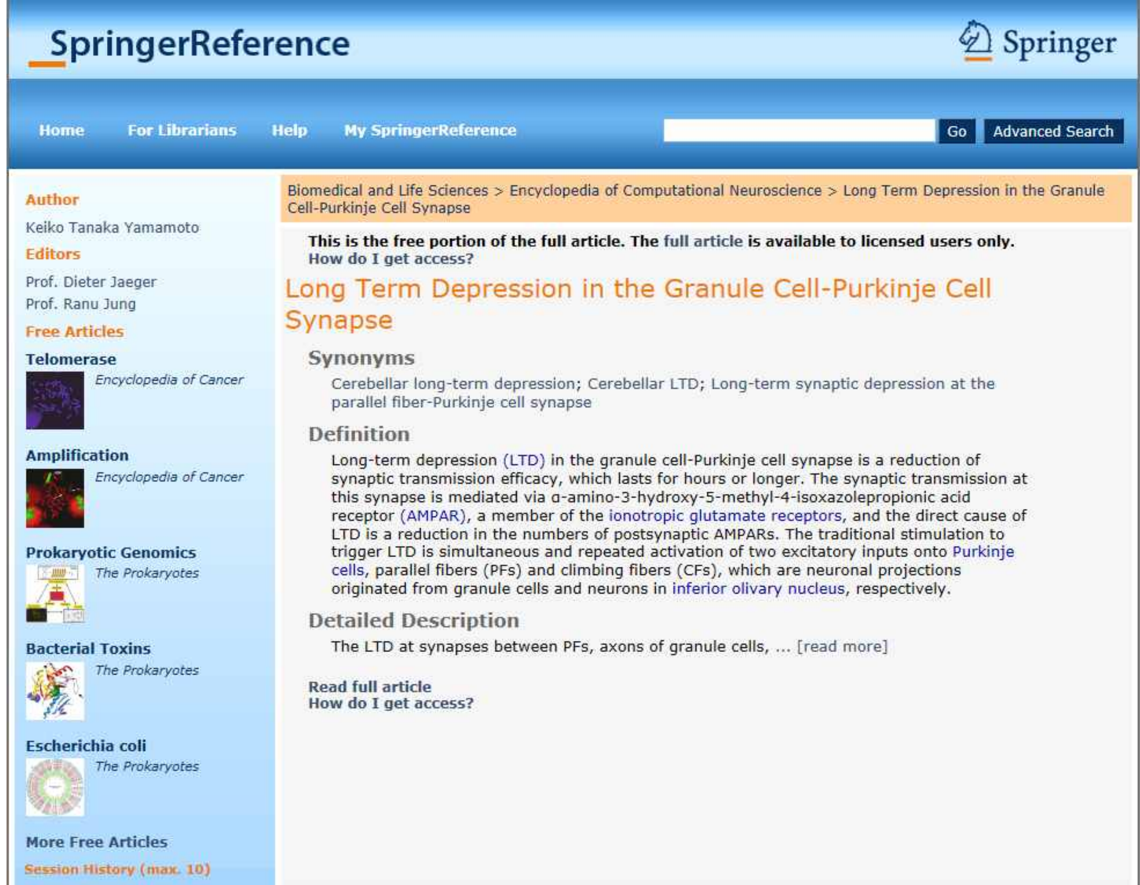

Long Term Depression in the Granule Cell-Purkinje Cell Synapse

Synonyms

Cerebellar long-term depression; Cerebellar LTD; Long-term synaptic depression at the parallel fiber-Purkinje cell synapse

Definition

Long-term depression (LTD) in the granule cell-Purkinje cell synapse is a reduction of synaptic transmission efficacy, which lasts for hours or longer. The synaptic transmission at this synapse is mediated via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), a member of the ionotropic glutamate receptors, and the direct cause of LTD is a reduction in the numbers of postsynaptic AMPARs. The traditional stimulation to trigger LTD is simultaneous and repeated activation of two excitatory inputs onto Purkinje cells, parallel fibers (PFs) and climbing fibers (CFs), which are neuronal projections originated from granule cells and neurons in inferior olivary nucleus, respectively.

Detailed Description

The LTD at synapses between PFs, axons of granule cells, and Purkinje cells (Fig. 1) was first discovered in the 1980s, and the observations of LTD have lead to the Marr-Albus-Ito theory (Marr 1969; Albus 1971; Ito 1986), in which some forms of cerebellum-dependent motor learning depend on long-term changes in synaptic transmission at these synapses. Long-term changes, reduction (LTD) or potentiation (LTP), in synaptic transmission efficacy, which is so-called long-term synaptic plasticity, have been observed in a variety of synapses in the brain. Indeed, the synapses between PFs and Purkinje cells could undergo not only LTD but also LTP (Lev-Ram et al. 2002). Such individual forms of long-term synaptic plasticity in several brain areas have their own molecular mechanisms or characteristic features, even though the final outcomes are either reduction or potentiation in synaptic transmission efficacy. Roles of long-term synaptic plasticity are further complicated, although they are mainly thought to be related to learning and memory. Therefore, it is important to know details of individual forms of long-term synaptic plasticity.

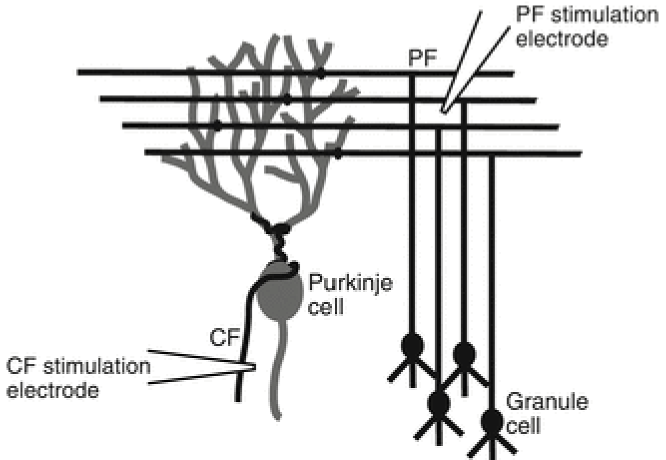

Fig. 1
A schematic illustration of two excitatory inputs onto Purkinje cells, CF and PF. Traditional stimulation to induce LTD is simultaneous and repeated stimulation of CF and PF through glass electrodes

There are several ways to describe details of LTD in the granule cell-Purkinje cell synapse, such as history of LTD, mathematical description of LTD, or argument regarding the behavioral functions of LTD. In this description, LTD will be

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explained mainly from a standpoint of signaling mechanisms and molecules related to the LTD (Fig. 2).

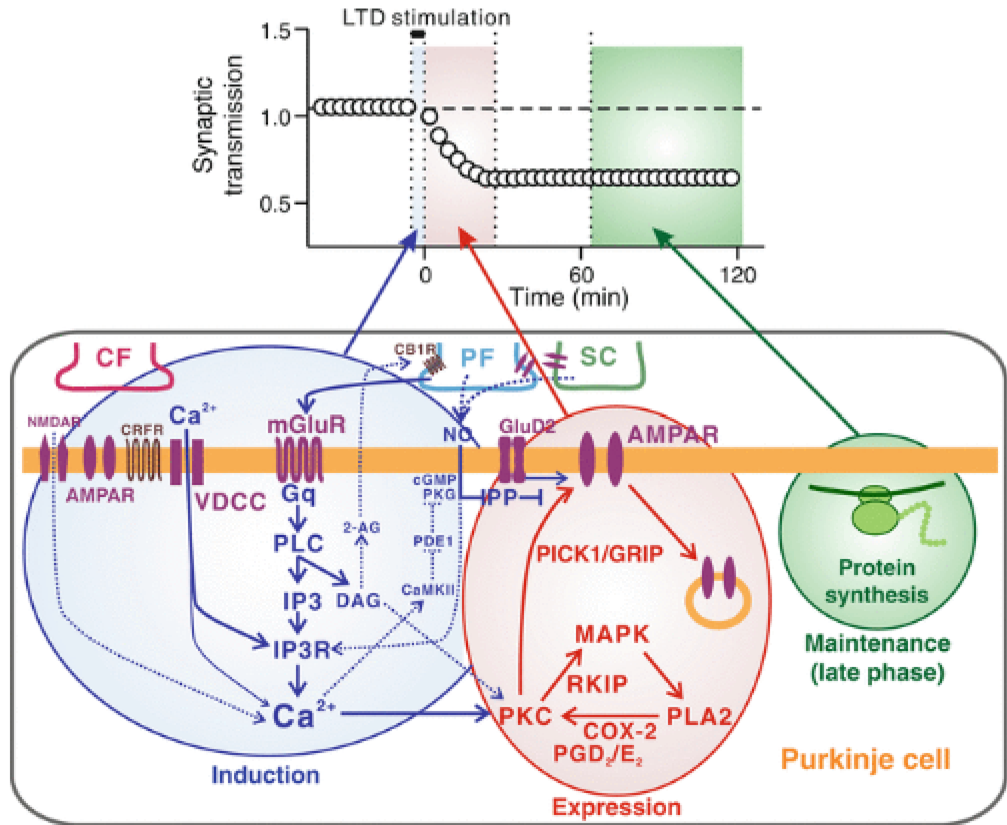

Fig. 2
A schematic illustration of time course of LTD and signaling mechanisms of LTD induction, expression, and maintenance. See text for abbreviations

Stimuli to Trigger LTD

Based on a theory of Albus and Marr (Marr 1969; Albus 1971), who postulated that CFs, another excitatory input onto Purkinje cells (Fig. 1), provide a teaching signal that induces long-term changes in the efficacy of PF-Purkinje cell synapses, stimulation to induce synaptic plasticity at these synapses was explored. Then it was discovered that LTD can be induced when simultaneous and repeated stimulations of PFs and a CF were applied in vivo or in cerebellar slice preparations. In most cases, these stimulations are applied electrically via glass electrodes (Fig. 1). Optimal conditions of such stimulation were also explored. Karachot et al. tested several conditions of stimulation in slice preparations, and they found that simultaneous stimulation of PF and CF at 1 Hz with 300 pulses most effectively induced LTD in terms of amounts and probability of depression (Karachot et al. 1994). Interestingly, similar stimulation with more pulses (500 pulses) is much less effective than 300 pulses. Further, timing between PF and CF stimulation seems to be critical, although precise interval is varied depending on other parameters of stimulation. Specifically, three studies have shown that LTD was effectively induced when PF stimulation preceded CF stimulation with approximately 100 ms, but LTD is not observed by opposite order of stimulation (Chen and Thompson 1995; Wang et al. 2000a; Safo and Regehr 2008). It should be noted that PF stimulation paired with CF stimulation to induce LTD is composed of one pulse in some cases but of a few pulses in other cases. Considering the existence of optimal conditions, the temporally and quantitatively precise regulation of signaling mechanisms seems to be important for triggering LTD.
The LTD described here is a long-term reduction of synaptic transmission at PF-Purkinje cell synapses, so that synaptic transmission has to be measured for the LTD study. At synapses between PF and Purkinje cells, AMPARs mediate synaptic transmission. Since AMPARs are nonselective cation channels, excitatory postsynaptic potential or current (EPSP or EPSC) can be recorded when AMPARs are activated by glutamate released from PFs. Usually, EPSP or EPSC is recorded by electrophysiological methods, such as extracellular recordings or patch clamp recordings.

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Even though paired stimulation of PFs and CFs has been the traditional stimulation that triggers LTD, as understanding of signaling mechanisms of LTD progressed, other stimulations, which can bypass several pathways or directly activate signaling molecules, have been used to induce LTD. For example, depolarizing pulses of Purkinje cells through patch clamp pipette can be used instead of CF stimulation (Fig. 3; Crépel and Jaillard 1991; Konnerth et al. 1992), because CF stimulation actually results in the depolarization of Purkinje cells that is necessary for LTD. In addition to in vivo or in slice preparations, LTD was observed in cultured Purkinje cells, where there are no longer intact synaptic connections. In order to trigger LTD in cultured Purkinje cells, glutamate receptor agonists were applied while depolarizing Purkinje cells, probably on the idea that the agonists could mimic PF stimulation (Linden et al. 1991). Glutamate has been also utilized to apply LTD stimulation onto whole cerebellar slices, when more tissue samples are required for analyses, such as biochemical, histological, or molecular biological analyses. In these experiments, slices are treated with glutamate in high-potassium solutions, and such treatment, which can be called chemical LTD stimulation, indeed triggers LTD (Tanaka and Augustine 2008). Moreover, direct increase or activation of signaling molecules, such as increase in intracellular calcium (Ca^{2+}) concentrations or activation of protein kinase C (PKC), could induce LTD (Linden and Connor 1991; Lev-Ram et al. 1997a; Kondo et al. 2005; Tanaka et al. 2007). These alternative stimulations are convenient for certain experimental conditions, effective to show the importance of a specific signaling molecule, or useful to determine the interactions of molecules working for LTD. However, results obtained in different conditions or by different stimulations are sometimes inconsistent. In order to reconcile discrepancy and to fully understand LTD, we may need to consider whether the observations in certain conditions can be generalized in more physiological conditions.

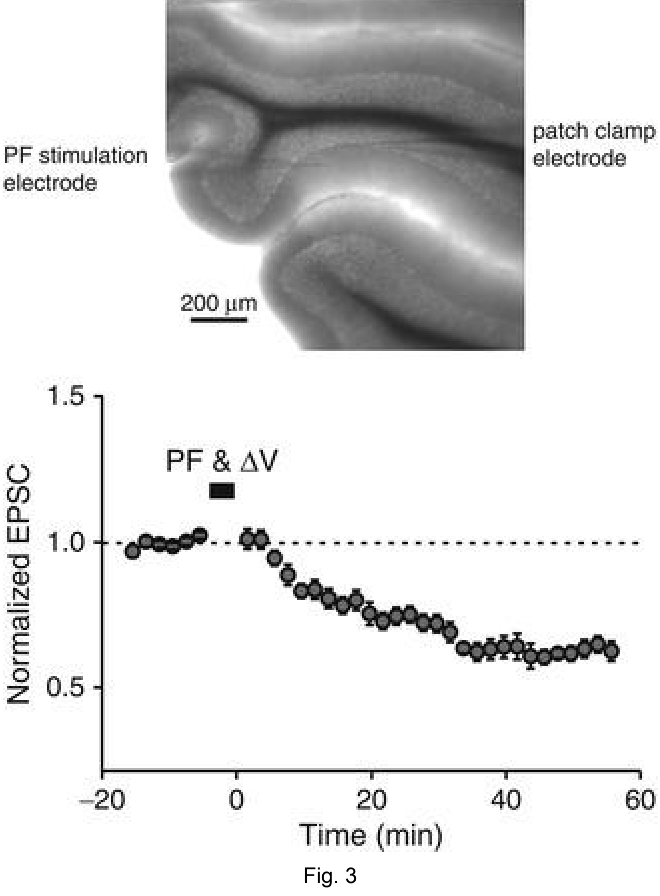

Fig. 3
An image of cerebellar slice showing the position of patch clamp electrode onto a Purkinje cell and the PF stimulation electrode (top), and time course of cerebellar LTD triggered by PF stimulation paired with Purkinje cell depolarization at 1 Hz for 5 min (bottom)

Time Course of LTD

Long-term synaptic plasticity, including cerebellar LTD, is generally composed of three temporal phases: induction, expression, and maintenance. The synaptic stimulation that triggers LTD usually lasts for a few to several minutes. During

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this period, the stimulation elevates or activates many signaling molecules, and this period of triggering LTD can be defined as the induction phase. The signaling molecules, which are elevated or activated during the stimulation, sequentially activate downstream molecules and finally cause the reduction of AMPAR numbers at synapses. This period when depression is in process is defined as the expression phase. The time course of expression varies according to stimulus conditions or preparations. In some cases, expression is rapid, so that depression reaches maximum level in a few minutes after the end of stimulation. In other cases, slow and gradual expression, which lasts for 20-60 min, can be observed. Mechanisms that determine the time course of LTD expression are not yet understood. Once depression reaches a maximum level, the depressed level is maintained for a few hours or even longer. The maintenance phase is often divided into early and late phases, latter of which is thought to depend on newly protein synthesis. It is not known whether the depression is terminated and synaptic transmission is returned to the original level after a certain period.

Fast Signals Required for the Induction of LTD

The well-studied and important signals required for the induction of cerebellar LTD are increases in postsynaptic Ca^{2+} concentrations ($[Ca^{2+}]_i$). The importance of $[Ca^{2+}]_i$ increase is first demonstrated in the experiments, where Ca^{2+} chelators, EGTA or BAPTA, were introduced into postsynaptic Purkinje cells (Sakurai 1990; Shibuki and Okada 1992; Konnerth et al. 1992). Such introduction of Ca^{2+} chelators blocks LTD. As mentioned above, the traditional stimulation that triggers LTD at least in cerebellar slice preparations can be the simultaneous and repeated stimulation of CFs and PFs. The stimulation of CFs or PFs causes increases in $[Ca^{2+}]_i$ in Purkinje cells (Konnerth et al. 1992; Eilers et al. 1997; Wang et al. 2000a). One Purkinje cell receives synaptic inputs from only one CF, but a pair of CF and Purkinje cell makes a few hundreds of synaptic connections. Thus, stimulation of CF activates many AMPARs at the CF and Purkinje cell synapses, so that the CF stimulation strongly depolarizes the innervated Purkinje cell, which in turn activates voltage-dependent Ca^{2+} channels (VDCCs) and induces Ca^{2+} entry through these channels (Ross and Werman 1987; Miyakawa et al. 1992; Konnerth et al. 1992). In contrast, one PF makes only one synapse onto one Purkinje cell, while about 150,000 PFs innervate a single Purkinje cell. At synapses between PFs and Purkinje cells, metabotropic glutamate receptor 1 (mGluR1) exists (Nusser et al. 1994; Baude et al. 1993; Petralia et al. 1998; López-Bendito et al. 2001) and is required for triggering LTD (Aiba et al. 1994; Conquet et al. 1994; Ichise et al. 2000). The mGluR1 is a type of receptor that is coupled with Gq-proteins, whose activation produces inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) via phospholipase C (PLC). The IP3 produced by PF activity binds and activates IP3 receptors on the endoplasmic reticulum, which is an intracellular Ca^{2+} store, so that $[Ca^{2+}]_i$ is increased by Ca^{2+} release through IP3 receptors. Such Ca^{2+} release from IP3 receptors is required for LTD (Khodakhah and Armstrong 1997; Inoue et al. 1998; Finch and Augustine 1998; Miyata et al. 2001). Although these pathways of $[Ca^{2+}]_i$ increase by PF and CF stimulation are superficially distinct, they also cooperate to induce larger $[Ca^{2+}]_i$ increase. Because paired stimulation of CFs and PFs, but not the stimulation of only CFs or PFs, induces LTD, it has been studied how the coincidence activation of two synaptic inputs is detected. One of the coincidence detection mechanisms is synergistic activation of IP3 receptors by IP3 and Ca^{2+} (Wang et al. 2000a; Doi et al. 2005; Sarkisov and Wang 2008), which are produced by PF stimulation and are entered through VDCCs after CF stimulation, respectively. Thus, it seems that $[Ca^{2+}]_i$ increase can reach to the level that is enough for LTD induction, when stimulations of PFs and CFs are paired.

The question was how large $[Ca^{2+}]_i$ increase is required for LTD. Because $[Ca^{2+}]_i$ increase triggered by synaptic stimulation is temporally complex and other signaling pathways activated by such stimulation may affect LTD, it is difficult to define the precise $[Ca^{2+}]_i$ increase required for LTD. Nevertheless, several efforts have been made to know the $[Ca^{2+}]_i$ increase by PF or CF stimulation. $[Ca^{2+}]_i$ increase evoked by CF stimulation is reaching around several hundred nanomolar in a wide area of dendrites (Wang et al. 2000a; Schmidt et al. 2003; Sarkisov and Wang 2008). Although $[Ca^{2+}]_i$ increase evoked by PF stimulation vary depending on the number and frequency of stimulation, $[Ca^{2+}]_i$ increase produced by a single or a few pulses of PF stimulation, which is often used to induce LTD, could also reach several hundred nanomolar in a part of dendrites where stimulated PF innervates (Finch and Augustine 1998; Wang et al. 2000a

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). In contrast, paired stimulation of CF and PF produces supralinear $[Ca^{2+}]_i$ increase, reaching a few micromolar to 10 μM (Wang et al. 2000a; Brenowitz and Regehr 2005), which is higher than the sum of $[Ca^{2+}]_i$ increase produced by PF and CF stimulation alone. Even though the $[Ca^{2+}]_i$ increase evoked by single paired stimulation is transient, presumably a few hundred milliseconds, repetitive stimulation could also produces gradually elevated $[Ca^{2+}]_i$ plateau (Eilers et al. 1995, 1996; Takechi et al. 1998; Finch and Augustine 1998; Wang et al. 2000a), so that repetitive and transient $[Ca^{2+}]_i$ increase is superimposed on such $[Ca^{2+}]_i$ plateau.

In order to define precise $[Ca^{2+}]_i$ required for triggering LTD, relationships between $[Ca^{2+}]_i$ increase and LTD were determined by using caged Ca^{2+}, which can release Ca^{2+} when photolysis is applied (Tanaka et al. 2007). The monotonic increase in $[Ca^{2+}]_i$ was produced by the photolysis of caged Ca^{2+} introduced into Purkinje cells, and the resultant LTD was measured. The relationships can be described by Hill equation with Hill coefficient of around 5, so that there is a threshold of $[Ca^{2+}]_i$ for triggering LTD. Further, in this series of experiments, several durations of $[Ca^{2+}]_i$ increase were tested. It was found that the $[Ca^{2+}]_i$ threshold of peak amplitude is higher when shorter duration of $[Ca^{2+}]_i$ increase is applied. In case that 0.5, 1, 15, or 30 s duration of photolysis was applied, $[Ca^{2+}]_i$ threshold is 2.8, 1.8, 1.1, or 0.9 μM, respectively. This suggests that peak $[Ca^{2+}]_i$ is not an absolute determinant for LTD. In contrast, more integrated $[Ca^{2+}]_i$ is necessary when longer duration of $[Ca^{2+}]_i$ increase is applied. The relationship between the threshold level of integrated $[Ca^{2+}]_i$ for LTD and duration of $[Ca^{2+}]_i$ increase fits to the leaky integrator property, similar to the "leaky integrate and fire" concept used in models of neuronal electrical signaling (Knight 1972; Fohlmeister et al. 1977). The leaky integrator for Ca^{2+}-triggered LTD can be expressed by an equation:

$$\tau\frac{dx}{dt}=-x+a\left[\mathrm{Ca}^{2+}\right]_i(t)$$

where τ is the time constant of the integration, x is the amount of a hypothetical downstream signal that transduces Ca^{2+} into LTD, and a is a scaling factor representing the efficacy of the integrator in converting Ca^{2+} into x. This suggests that, while $[Ca^{2+}]_i$ increase activates molecules that positively work for LTD, negative regulators seem to gradually become active during longer duration of $[Ca^{2+}]_i$ increase. The leaky integrator property of LTD triggering may be the reason why 500 pulses of paired stimulation of PF and CF are less effective than 300 pulses (Karachot et al. 1994). Thus, the analysis using caged Ca^{2+} defined $[Ca^{2+}]_i$ required for LTD, which depends on the duration of $[Ca^{2+}]_i$ increase.

In addition to Ca^{2+}-related signals described above, the stimulation of PF and CF could elevate or activate other signals that are superficially independent to these Ca^{2+} signals. PF stimulation can trigger the release of nitric oxide (NO) from PF terminals or stellate cells (Shibuki and Okada 1991; Lev-Ram et al. 1997b; Namiki et al. 2005), the latter of which are interneurons in the molecular layer. Several studies demonstrated that NO is involved in LTD (Ito and Karachot 1990; Crépel and Jaillard 1990; Shibuki and Okada 1991; Daniel et al. 1993; Lev-Ram et al. 1995; Reynolds and Hartell 2001). Although NO cannot induce LTD by itself, NO cooperates with subthreshold level of Ca^{2+}, which is not sufficient to induce LTD (Lev-Ram et al. 1995, 1997a), so that NO is considered to play a permissive role for LTD. Considering that NO is generally known to activate guanylate cyclase (GC) (Jaffrey and Snyder 1995; Calabrese et al. 2007), the roles of NO for LTD are thought to be as follows. NO released from PF or stellate cells diffuses into Purkinje cells and activates GC, which produces cyclic guanosine monophosphate (cGMP). The cGMP activates cGMP-dependent protein kinase (PKG), which reduces protein phosphatase 2A (PP2A) activities. Phosphorylation of molecules, such as AMPARs, is necessary for LTD, so that the reduction of PP2A activities positively works for LTD. In fact, inhibition of GC or PKG blocked LTD, and inhibition of PP2A itself could induce synaptic depression (Ito and Karachot 1990; Hartell 1994; Reynolds and Hartell 2001; Endo et al. 2003; Launey et al. 2004). These results suggest that this NO-mediated pathway is likely one mechanism working for LTD induction. Further, because it is reported in other types of cells that cGMP facilitates Ca^{2+}

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release from IP3 receptors via PKG activation (Guihard et al. 1996; Rooney et al. 1996; Wagner et al. 2003) and the IP3-dependent Ca^{2+} release is critical for cerebellar LTD (Khodakhah and Armstrong 1997; Inoue et al. 1998; Finch and Augustine 1998; Miyata et al. 2001), a pathway of NO, cGMP, and PKG may also contribute to induce higher $[Ca^{2+}]_i$ increase. Thus, NO may have dual roles for LTD induction.

Another molecule released upon the PF stimulation is endocannabinoid, which is known as a retrograde messenger. In the cerebellar cortex, 2-arachidonoyl glycerol (2-AG) is released from Purkinje cells (Maejima et al. 2005). Because local $[Ca^{2+}]_i$ increase due to AMPAR-mediated depolarization and mGluR1 activation cooperatively produce endocannabinoid (Maejima et al. 2001; Brown et al. 2003; Marcaggi and Attwell 2005), relatively strong PF stimulation, such as a brief burst of PF stimulation, seems to trigger the release of 2-AG. 2-AG is produced by diacylglycerol lipase from DAG (Sugiura et al. 2006), which is produced by PLC after the activation of mGluR1 and Gq-protein. Because the PLC, specifically PLCβ4, is also sensitive to Ca^{2+}, strong PF stimulation activates PLCβ4 via Gq-protein and Ca^{2+} and in turn leads to 2-AG release via DAG production (Maejima et al. 2005). The function of endocannabinoid as a retrograde messenger has been well studied to explain the mechanism of short-term synaptic depression at PF and Purkinje cell synapses (Maejima et al. 2001; Brown et al. 2003; Marcaggi and Attwell 2005), which depends on the reduction of glutamate release via presynaptic cannabinoid receptor type 1 (CB1R) (Yoshida et al. 2002). Endocannabinoid signaling is also involved in cerebellar LTD, because LTD was impaired in the presence of a CB1R antagonist or a diacylglycerol lipase inhibitor or in CB1R knockout mice (Safo and Regehr 2005). Further, LTD was not observed even in mice lacking CB1Rs selectively in cerebellar granule cells (Carey et al. 2011). It is known that LTD is postsynaptically induced, so that it remains elucidated how retrograde endocannabinoid signaling and presynaptic CB1Rs affect postsynaptically induced LTD.

Corticotropin-releasing factor (CRF) exists in the CF (Palkovits et al. 1987; Sakanaka et al. 1987; Cummings et al. 1994), so that CRF can be released from CF terminals. On the other hand, mRNA of CRF receptors is detected in Purkinje cells (Chang et al. 1993; Potter et al. 1994). A study demonstrated that antagonists of CRF receptors blocked not only LTD induced by conjunctive stimulation of PF and CF but also LTD induced by the pairing of PF stimulation with Purkinje cell depolarization (Miyata et al. 1999). Further, LTD was not observed in animals, whose CF was chronically destructed, but it was restored by CRF replenishment (Miyata et al. 1999). According to these results, it is thought that spontaneously released CRF from CF, rather than CRF released by CF stimulation during LTD induction, plays a permissive role in LTD.

As described above, DAG is produced via mGluR activation. Although there has been no direct evidence showing that DAG produced by mGluR activation is truly required for LTD, DAG may cooperate with Ca^{2+} to activate downstream molecules, such as PKC, or may contribute to produce 2-AG.

Mechanisms Required for Expression of LTD

The expression of LTD correlates with a reduction in the number of synaptic AMPARs, and the reduction is due to the enhancement of AMPAR internalization by clathrin-mediated endocytosis (Wang and Linden 2000). The enhancement of AMPAR internalization is triggered by PKC-dependent phosphorylation of GluR2, an AMPAR subunit, at serine 880 (Ser880) (Matsuda et al. 2000; Xia et al. 2000; Chung et al. 2003). While dephosphorylated GluR2 interacts with glutamate receptor-interacting protein/AMPA receptor-binding protein (GRIP/ABP), which is the postsynaptic density-95/discs-large/zonula occludens-1 (PDZ) domain-containing protein, via PDZ-binding motif of GluR2, such interaction is prevented by the PKC-dependent phosphorylation of GluR2 (Matsuda et al. 2000; Xia et al. 2000). The unbinding of GRIP/ABP itself or the following interaction of phosphorylated GluR2 with another PDZ domain-containing protein, PICK1, leads to the endocytosis of AMPARs (Steinberg et al. 2006).

Among several subtypes of PKC, PKCα has been shown to be responsible for the LTD, because knockdown of PKCα blocked LTD (Leitges et al. 2004). Given that PKCα is a Ca^{2+}-dependent form of PKC, it is likely that PKCα is activated by Ca^{2+}. However, even though such a Ca^{2+}-dependent PKCα activation might be sufficient for the AMPAR internalization during rapid expression of LTD, it cannot explain the gradual expression of LTD, which is often observed, because $[Ca^{2+}]_i$ increase is transient (Konnerth et al. 1992; Eilers et al. 1997; Tanaka et al. 2007). To fill the temporal gap, a positive feedback kinase loop is shown to be responsible for the prolonged PKC activation and consequently gradual expression of LTD (Kuroda et al. 2001; Tanaka and Augustine 2008). This loop includes several molecules. PKC phosphorylated Raf-kinase inhibitory protein (RKIP). RKIP usually binds and inhibits Raf1 and MEK, which are upstream kinases of migoten-activated protein kinase/extracellular-signal-regulated kinase (MAPK/Erk), but phosphorylated RKIP

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dissociates from these molecules, so that the Raf1-MEK-MAPK pathway can be activated (Yamamoto et al. 2012). MAPK directly phosphorylates and activates phospholipase A2 (PLA2), and PLA2 produces arachidonic acid, which can activate PKC directly or indirectly via cyclooxygenase-2 and prostaglandin D_2 or E_2 (Le et al. 2010). Thus this loop can extend the timing of PKC activation, so that LTD is gradually expressed.

As described above, it is well known that PKC-dependent phosphorylation of GluR2 AMPARs is important for LTD. However, it is not known whether other molecules in the positive feedback loop have roles in LTD, except for working as components of this loop. Specifically, since MAPK generally has many target molecules and is involved in several cellular events, it is interesting to elucidate another function of MAPK in LTD.

Involvement of this positive feedback loop fits well to the time course of gradual expression of LTD. Although it is not clear whether this loop is also required for LTD with rapid expression, this loop and similar regenerative system may be generally attractive mechanisms for long-term synaptic plasticity. One of the important aspects of long-term synaptic plasticity is that such plasticity is generally triggered by transient synaptic stimulation but lasts for a long time, so that some mechanisms seem to work for the temporal conversion from transient stimulation to long-term signaling activities. The positive feedback loop working for the cerebellar LTD is likely one example of such mechanisms.

Mechanisms Required for Maintenance of LTD

Compared with the induction and expression, considerably less is known about mechanisms required for LTD maintenance. Nevertheless, studies using cultured Purkinje cells demonstrated the 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, the cyclic AMP (cAMP)-responsive element-binding protein (CREB) and the Ca^{2+}-/calmodulin-dependent protein kinase type IV (CaMKIV), were implicated in this phase (Ahn et al. 1999), although it is not clear which transcripts are regulated by these transcriptional regulators. Another transcriptional regulator, serum response factor (SRF), was also implicated in the late phase of LTD. In case of SRF, a target transcript is also shown. SRF binds to the SRE 6.9 site in the promoter region of the synaptic protein Arc, so that Arc is expressed in an SRF-dependent manner (Smith-Hicks et al. 2010). Further, the late phase of LTD is reported to require persistent dynamin-mediated endocytosis, which may also depend on Arc expression (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 whether or when newly synthesized protein-dependent late-phase LTD is initiated in slice preparations, because bath application of translational inhibitors already blocks its induction (Karachot et al. 2001). Even if we assume that similar mechanisms observed in cultured Purkinje neurons account for the maintenance of the late phase of LTD in intact cerebellar networks, it still has to be elucidated how early maintenance between the expression phase and late phase is achieved. A conceptual model and an analysis of experimental results suggest that another type of bistable switch, which shows threshold behavior, works after the positive feedback loop described above (Kawato et al. 2011; Kim and Tanaka-Yamamoto 2013).

Spatial Aspects of LTD

Spatial aspects of long-term synaptic plasticity can be represented by homosynaptic and heterosynaptic plasticity. Long-term synaptic plasticity is typically input-specific, meaning that long-term changes in synaptic transmission occur only in synapses, where synaptic plasticity-inducing activities are applied. This is called homosynaptic plasticity. In contrast, when synaptic plasticity is triggered at synapses, where activities are not applied, this is called heterosynaptic plasticity. While cerebellar LTD appears to be homosynaptic when LTD is induced by pairing weak PF activity with CF activity (Wang et al. 2000a), it has also been shown that cerebellar LTD induced by pairing stronger PF activity with CF activity can spread to nearby inactive PF synapses (Wang et al. 2000b; Reynolds and Hartell 2000). Mechanisms of this heterosynaptic LTD are not understood. One suggestion arose from experiments of LTD induced by uncaged Ca^{2+}. The uncaged Ca^{2+}-induced LTD does not spread beyond the area of $[Ca^{2+}]_i$ increase (Tanaka et al. 2007), so that downstream signals of Ca^{2+} are unlikely key factors for spreading LTD, although they may cooperate with other molecules, such as IP3 or lower concentration of $[Ca^{2+}]_i$. Since NO is a gas messenger, NO was thought to be a

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candidate of spreading molecules (Reynolds and Hartell 2001), yet it was demonstrated that NO released by PF stimulation did not spread as expected (Namiki et al. 2005).

Other Signaling Mechanisms Involved in LTD

Although many molecules are already discussed in this description, there are still several other molecules that have been shown to be involved in LTD. Some of them are introduced below.

A member of ionotropic glutamate receptor, δ2 glutamate receptor (GluD2 or GluR δ2), is predominantly expressed on the postsynaptic sites of synapses between PFs and Purkinje cells (Landsend et al. 1997; Zhao et al. 1998). In GluD2-null mice, the numbers of PF-Purkinje cell synapses are severely reduced (Kurihara et al. 1997; Lalouette et al. 2001) and LTD is impaired (Kashiwabuchi et al. 1995; Motohashi et al. 2007), so that GluD2 has two functions on PF-Purkinje cell synapses. These two functions are distinct, because expression of mutant GluD2, which lacks a PDZ ligand domain at C-terminus, rescued the morphological abnormality, but not the impairment of LTD (Uemura et al. 2007; Kakegawa et al. 2008). Unlike other ionotropic glutamate receptors, such as AMPARs, GluD2 does not normally function as an ion channel for LTD (Kakegawa et al. 2007), even though GluD2 is included as a member of ionotropic glutamate receptor. Instead, the C-terminal PDZ ligand domain of GluD2 has functions to regulate intracellular signaling. It is indeed demonstrated that GluD2 interacts with the tyrosine phosphatase PTPMEG via the PDZ ligand domain and regulates phosphorylation of GluR2 AMPARs at tyrosine 876 (Tyr876) (Kohda et al. 2013). The dephosphorylation of Tyr876 of GluR2 via GluD2 and PTPMEG allows GluR2 to be phosphorylated at Ser880, which is required for LTD. Thus, GluD2 gates the LTD by coordinating interactions between two phosphorylation sites of GluR2.

Another type of ionotropic glutamate receptor, N-methyl-D-aspartate receptor (NMDAR), is critical in many forms of synaptic plasticity. However, NMDAR was originally excluded from mechanisms of cerebellar LTD, because it was believed that NMDAR was not expressed in Purkinje cells, based on studies using young animals (Perkel et al. 1990; Llano et al. 1991). On the other hand, when adult animals were used, the expression of NMDAR was detected at postsynaptic sites of CF-Purkinje cell synapses (Piochon et al. 2007; Renzi et al. 2007). Then, it is demonstrated that NMDAR at CF-Purkinje cell synapses contributes to the CF-dependent $[Ca^{2+}]_i$ increase and LTD in adult animals (Piochon et al. 2010). In addition, NMDAR at presynaptic sites of PF terminals or stellate cells are also shown to be involved in LTD (Casado et al. 2002; Shin and Linden 2005).

For the hippocampal LTP, calcium-/calmodulin-dependent protein kinase II (CaMKII) has been intensively studied, and it is indeed demonstrated that CaMKII is an important mediator for LTP (Lisman et al. 2012). The involvement of CaMKII in cerebellar LTD was not investigated for a long time, probably because other kinases, specifically PKC, have been already shown to be critical for LTD. Yet it was demonstrated that αCaMKII knockout mice show impairment of LTD or even show LTP upon the stimulation that usually triggers LTD in wild-type mice (Hansel et al. 2006). Further, βCaMKII knockout mice show opposite direction of synaptic plasticity: LTP is triggered by a stimulation that usually triggers LTD in wild-type mice, while LTD is triggered by a stimulation that usually triggers LTP in wild-type mice (van Woerden et al. 2009). Detailed mechanisms of these phenomena were not fully understood. However, a combined study of computational model and experiments using cultured Purkinje cells proposed that CaMKII gates LTD by reducing PP2A activities via several steps (Kawaguchi and Hirano 2013). In their model, CaMKII negatively regulate phosphodiesterase1 (PDE1), which degrades cGMP and consequently reduces PKG activities. Thus, negative regulation of PDE1 by CaMKII leads to PKG activation, which in turn reduces PP2A activities. The pathway of cGMP-dependent PKG activation is triggered by NO, as mentioned above, so that NO seems to be capable of compensating the lack of CaMKII activities.

Kinetic Model of LTD

Mathematical description is not a focus of this description, so that details of computational model are not described here. However, it is probably worth to mention the contribution of computational models of kinetic simulations. As described here, signaling mechanisms of LTD are complex and many molecules are implicated in LTD. To systematically understand the interaction of molecules and characteristic aspects produced by these signaling mechanisms, a computational model of kinetic simulation has been effective. A kinetic model indeed first incorporated the positive feedback loop of PKC and MAPK as a mechanism to expand the timing of PKC and MAPK activation as well as AMPAR phosphorylation (Kuroda et al. 2001). This model also succeeded to reproduce the permissive role of NO. A slightly

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modified version of this model was then used to explain the relationship between $[Ca^{2+}]_i$ and LTD (Tanaka et al. 2007). Then the model suggested that the sigmoidal relationship arose at least in part from the positive feedback loop. Although this model reproduces most of features in the relationship, there is one feature that the model predicts differently from experimental results. The slope of sigmoidal curve for the relationship is steeper in the model than that in the experimental results. In other words, the model predicts all-or-none induction of LTD, while intermediate level of LTD is observed in experiments. However, if the distribution and noise of $[Ca^{2+}]_i$ increase are considered, a similar curve could be obtained. In contrast, another computational study considered stochastic features of signaling in LTD by taking into account only a few tens of molecules being involved in the LTD process within a confined region like a dendritic spine (Antunes and De Schutter 2012). This stochastic model actually reproduces experimental relationship between $[Ca^{2+}]_i$ and LTD without including the effects of distribution and noise of $[Ca^{2+}]_i$ increase. Thus, it may be interesting to directly test such stochastic features by experiments.

Postsynaptic LTD and LTP

In addition to LTD, two forms of LTP can be also triggered at the PF-Purkinje cell synapses. One is presynaptic LTP, which is induced by a few minutes of PF stimulation at 4 Hz. This presynaptic LTP is mediated by cAMP and protein kinase A (PKA) and relies on the potentiation of glutamate release (Salin et al. 1996). Because LTD is postsynaptically induced and expressed, it was believed that there should be postsynaptic LTP as a mechanism of resetting LTD. Indeed, another form of LTP is postsynaptic LTP (Lev-Ram et al. 2002), which seems to depend on GluR2 trafficking (Kakegawa and Yuzaki 2005). The LTP is induced by 5 min of PF stimulation at 1Hz and requires NO, but not cAMP, PKA, cGMP, or PKG. In clear contrast to LTD, this LTP requires the activation of protein phosphatases (PPs), PP1, PP2A, and PP2B (Belmeguenai and Hansel 2005). As expected, LTD can be canceled, when this LTP protocol is applied after LTD is saturated. Oppositely, when LTD protocol is applied after LTP is saturated, LTP can be canceled (Lev-Ram et al. 2003; Coesmans et al. 2004). Thus the postsynaptic LTD and LTP reset each other.
The postsynaptic LTD can be triggered by 5 min of PF stimulation at 1 Hz with concomitant CF stimulation, while the postsynaptic LTP can be triggered by the same PF stimulation without concomitant CF stimulation. It has been discussed regarding the signaling mechanisms to distinct LTP and LTD. Because CF stimulation is the difference between stimulation causing LTD and LTP, one idea is that Ca^{2+} concentration during stimulation may determine the direction of synaptic plasticity. Relatively higher concentrations of $[Ca^{2+}]_i$ increase is required and is even sufficient for LTD. In contrast, LTP is blocked by 15-30 mM BAPTA, a Ca^{2+} chelator, but not by 5 mM BAPTA (Coesmans et al. 2004). This indicates that lower concentration of Ca^{2+} seems to be necessary for LTP, although it is not clear whether $[Ca^{2+}]_i$ increase is required or basal level of $[Ca^{2+}]_i$ is enough for LTP. Based on these results, "inverse BCM rule" has been proposed (Coesmans et al. 2004). BCM stands for Bienenstock, Cooper, and Munro, who originally proposed the "BCM rule," which is a theory to describe how the threshold of synaptic plasticity is determined (Bienenstock et al. 1982). Based on the BCM rule, lower and higher $[Ca^{2+}]_i$ increases are associated with the induction of LTD and LTP, respectively. In case of PF-Purkinje cell synapses, the requirement of $[Ca^{2+}]_i$ for LTD and LTP is opposite, so that "inverse BCM rule" was proposed. However, because LTD, but not LTP, was observed by $[Ca^{2+}]_i$ increase upon uncaging Ca^{2+}, the amplitude of $[Ca^{2+}]_i$ may not be a sole factor to determine the direction of synaptic plasticity in PF-Purkinje cell synapses. Probably, the combination of Ca^{2+} signals with other signals, such as NO, balances the activities of protein phosphatases and kinases and consequently triggers either LTD or LTP (Lee 2006).

Roles of LTD

Even though LTD was originally found as a cellular basis of motor learning, the relationship between LTD and motor learning is still controversial. In many studies using genetically modified animals, in which signaling molecules required for LTD are modified, it has been demonstrated that motor learning is impaired in these animals (Yuzaki 2012). These studies support the idea that LTD is important for motor learning. In contrast, there are also reports showing discrepancy

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between cerebellar LTD and motor leaning. For example, in mice that do not show LTD due to the genetic modification causing inhibition of AMPAR internalization in Purkinje cells, several types of motor learning were intact (Schonewille et al. 2011). Thus, the relationship between LTD and motor learning has to be further elucidated. However, if LTD would not play a role in motor learning, the question is what would be the roles of LTD. Given that LTD is induced by the conjunctive stimulation of two excitatory inputs and is precisely regulated by many signaling molecules, it is difficult to imagine that LTD does not have any functions. LTD seems to have at least an impact on the function of cerebellar neural networks, because it was reported that 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).

Cross-References

CaMKII
cAMP
cGMP
Clathrin
Corticotropin-Releasing Factor
CREB
Cyclooxygenase-2
GluD2
Diacylglycerol
Endocannabinoid
Endocytosis
Endoplasmic Reticulum
EPSP
Extracellular Recording
Glutamate Receptors
Gq-Protein
Guanylate Cyclase
Heterosynaptic
Hill Coefficient
Hill Equation
Homosynaptic
Inositol 1,4,5-trisphosphate
IP3 Receptors
Learning and Memory
LTD
MAPK
MEK
Metabotropic Glutamate Receptor
Motor Learning
Nitric Oxide
NMDAR
Patch Clamp
PDZ Domain
Phospholipase
Photolysis
Protein Kinase A
Protein Kinase C
Phospholipase A2
PLC
PP2A
cGMP-dependent Protein Kinase

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Protein Phosphatase
Raf
Retrograde Messenger
RKIP
Slice Preparation
SRF
Synaptic Plasticity
Uncaging
Voltage-Dependent Ca^{2+} Channels
AMPAR

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Keiko Tanaka Yamamoto — Center for Functional Connectomics, Korea Institute of Science and Technology, Seoul, Republic of Korea

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