Chapter 43
Plasticity of the Cerebellum

Ying Shen

Abstract Since 1990s, long-term depression of (LTD) at parallel fiber-Purkinje cell synapses has been regarded as a cellular phenomenon for motor learning. However, parallel fiber LTD by itself cannot account for motor learning. Here, I review a rich variety of use-dependent plasticity in the cerebellar cortex and nuclei, including long-term potentiation (LTP) and LTD at excitatory and inhibitory synapses, and persistent modulation of intrinsic excitability. Intrinsic and extrinsic factors, including neuronal excitation, specific molecular mechanisms and theta oscillation, and external neuromodulators, are essential to different forms of plasticity.

Keywords Cerebellum • Long-term potentiation • Long-term depression • Purkinje cell • Motor learning

43.1 Parallel Fiber LTD

A persistent attenuation of parallel fiber-Purkinje cell synapse is produced when parallel fiber and climbing fiber inputs to a Purkinje cell are stimulated together at low frequency (Ito et al. 1982). The parallel fiber LTD is associative and saturable upon repeated parallel fiber stimulation. Strong parallel fiber stimulation or conjunctive climbing fiber/parallel fiber stimulation induces parallel fiber LTD through the activation of postsynaptic metabotropic glutamate receptors (mGluR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), and subsequent rise of internal Ca^{2+}. The activation of protein kinase Cα (PKCα) and α-Ca^{2+}/calmodulin-dependent protein kinase II (αCaMKII) are required. The cytosolic phospholipase A_2α (cPLA_2α)/cyclooxygenase-2 cascade plays important roles in this LTD by acting on upstream PKCα. Cannabinoid receptor 1 (CB1R) and nitric oxide/soluble guanylyl cyclase/cGMP-dependent protein kinase/phosphatase

---

Y. Shen (✉)
Department of Neurobiology, Zhejiang University School of Medicine,
Hangzhou 310058, People's Republic of China
e-mail: yshen@zju.edu.cn

D.L. Gruol et al. (eds.), *Essentials of Cerebellum and Cerebellar Disorders*,
DOI 10.1007/978-3-319-24551-5_43

pathways are also invovled (Bear and Linden 2000; Safo and Regehr 2005). Parallel fiber LTD is expressed postsynaptically, as a reduction in the number of surface AMPARs produced by clathrin-dependent endocytosis (Wang and Linden 2000).

43.2 Parallel Fiber LTP

Parallel fiber-Purkinje cell synapses undergo two forms of homosynaptic LTP, depending on stimulus frequency. Four to 8 Hz parallel fiber stimulation induces presynaptically-expressed LTP, which is associated with a decrease in paired-pulse facilitation (Salin et al. 1996) and evoked glutamate transport currents in glial cells (Linden 1998). Furthermore, 4–8 Hz LTP is mediated by the presynaptic adenylyl cyclase/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway (Hansel et al. 2001). Evidence from cerebellar cultures shows that 4-Hz LTP is mediated by PKA-mediated phosphorylation of the active zone protein RIM1α (Lonart et al. 2003).

In contrast, 1-Hz parallel fiber stimulation induces a postsynaptically-expressed LTP. This LTP requires a low level of Ca^{2+} in Purkinje cells (Coesmans et al. 2004), which leads to the activation of $cPLA_2\alpha$, the liberation of arachidonic acid, and the production of 2-arachidonoylglycerol (2-AG). Activated CB1R on presynaptic terminals by 2-AG triggers the activation of nitric oxide synthase and produces a low-level release of nitric oxide from parallel fiber terminals (Wang et al. 2014). Afterwards, nitric oxide works postsynaptically with serine/threonine phosphatases to promote the required trafficking of AMPARs. Since 1-Hz LTP and parallel fiber LTD are both expressed postsynaptically, it is suggested that 1-Hz LTP is a resetting mechanism for motor learning and causes the extinction of learned associations.

43.3 Climbing Fiber LTD

5 Hz tetanization of climbing fibers evokes a LTD at climbing fiber-Purkinje cell synapse, which is homosynaptic and saturable (Hansel and Linden 2000). Climbing fiber LTD requires intracellular Ca^{2+} and the activation of mGluR1 and PKC, and is expressed postsynaptically (Shen et al. 2002). Climbing fiber LTD is hypothesized to control the integrative response of Purkinje cell because complex spikes are attenuated after 5 Hz tetanization. Interestingly, 5 Hz tetanization at climbing fibers also induces a LTP of glutamate transporter EAAT4 (Shen and Linden 2005).

43.4 Interneuron-Purkinje Cell Synaptic LTP

LTP of $GABA_A$ receptor-mediated inhibitory postsynaptic currents in Purkinje cells is induced by repetitive climbing fiber activation (Kano et al. 1992). This inhibitory LTP requires a postsynaptic Ca^{2+} transient from internal Ca^{2+} stores and the activation of CaMKII and PKA. An early study showed that simultaneous activity of inhibitory synapses is needed for the induction of inhibitory LTP (Kano 1996), but another study showed that simultaneous inhibitory activity suppresses the inhibitory LTP (Kawaguchi and Hirano 2000). Interneuron-Purkinje cell synaptic LTP has a major influence on Purkinje cells throughput, as it modulates the spike firing pattern in Purkinje cells (Häusser and Clark 1997).

43.5 Plasticity of Mossy Fiber-Granule Cell Synapses

Mossy fiber-granule cell synapses provide a large potential substrate for information storage. Activation of mossy fibers combined with postsynaptic depolarization of granule cells results in mossy fiber LTP (D'Angelo et al. 1999), which requires postsynaptic depolarization, Ca^{2+} influx and activation of NMDA receptors, mGluR, and PKC. The inhibitory input by Golgi cells also affects the expression of mossy fiber LTP. In contrast, protracted low-frequency stimulation causes mossy fiber LTD (Gall et al. 2005). Mossy fiber LTP and LTD promote the population (summated) and sparse (local) coding, respectively, in the granular layer.

43.6 Plasticity in the Deep Cerebellar Nuclei (DCN)

Mossy fiber-DCN plasticity depends on the excitation of DCN cells (Pugh and Raman 2006) while Purkinje cell-DCN plasticity depends on the excitation of both DCN cells and Purkinje cells (Aizenman et al. 1998). DCN cells can also generate a plasticity of intrinsic excitability. Mossy fiber-DCN plasticity and intrinsic excitability can work together to generate a coincidence detector driven by intracellular calcium transients.

43.7 Plasticity of Intrinsic Excitability in Purkinje Cells

Purkinje cell excitability can be enhanced by somatic current injections or parallel fiber stimulation. Signal cascades for LTP of intrinsic excitability include local Ca^{2+} in spines and protein phosphatases. The interactions between these molecules and PKA and casein kinase 2 result in a downregulation of small conductance Ca^{2+}-activated potassium channels, thereby reducing an intrinsic inhibitory influence. LTP of intrinsic plasticity occludes subsequent parallel fiber LTP, but facilitates parallel fiber LTD (Coesmans et al. 2004). LTP of intrinsic plasticity can be locally restricted to one synapse, but can also affect a large number of synapses, depending on the identity and location of intrinsic conductances altered.

43.8 Spike-Timing Dependent Plasticity (STDP) in Cerebellum

Since the first report by Ekerot and Kano (1989), a series of studies have determined that parallel LTD is induced best when parallel fiber stimulation precedes climbing fiber-evoked complex spikes in Purkinje cells by 50–250 ms, suggesting an anti-Hebbian STDP mechanism in the cerebellum. Cerebellar STDP differs from that at hippocampal synapses, in that it is independent of axonal spike output. Rather, external climbing fiber stimulation and locally elicited Ca^{2+} spikes play a key role.

43.9 Conclusions

It is clear now that cerebellar learning is an integrated process involving numerous forms of synaptic plasticity in the cerebellar cortex and nuclei, where various specific spatial patterns are organized. Channeling begins from granular layer and is concluded in the molecular layer, where Purkinje cells integrate signals from different inputs. Plasticity is also organized in specific temporal patterns in the granular and molecular layer. In this view, the mechanisms for cerebellar learning should be viewed as the integration of various plasticities in the cerebellar cortex and nuclei (Fig. 43.1).

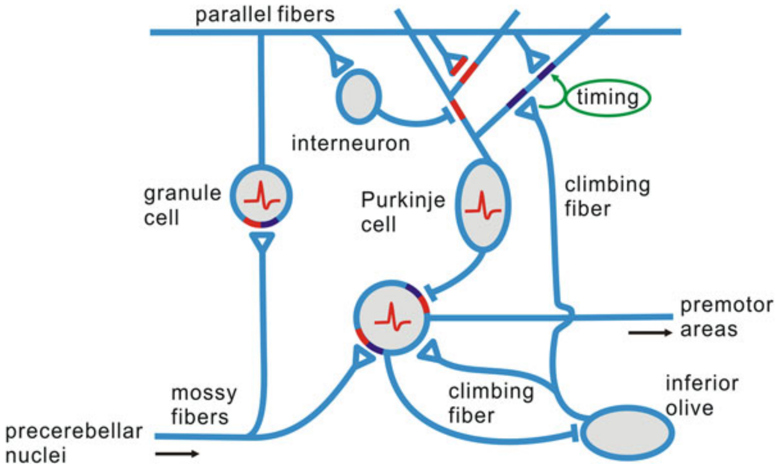

Fig. 43.1 A summary of plasticity in the cerebellar circuit (Modified with permission from Hansel et al. 2001). The occurrence of long-term plasticity is coded with color: *red* indicating potentiation and *blue* indicating depression. The intrinsic excitability is labeled with action potentials in somata, whereas conventional synaptic LTP or LTD is labeled with *bars of colors* at synapses

References

Aizenman CD, Manis PB, Linden DJ (1998) Polarity of long-term synaptic gain change is related to postsynaptic spike firing at a cerebellar inhibitory synapse. Neuron 21:827–835

Bear MF, Linden DJ (2000) The mechanisms and meaning of long-term synaptic depression in the mammalian brain. In: Cowan WM, Davies K (eds) The synapse. Johns Hopkins University Press, Baltimore, pp 455–516

Coesmans M, Weber JT, De Zeeuw CI et al (2004) Bidirectional parallel fiber plasticity in the cerebellum under climbing fiber control. Neuron 44:691–700

D'Angelo E, Rossi P, Armano S et al (1999) Evidence for NMDA and mGlu receptor-dependent long-term potentiation of mossy fibre–granule cell transmission in rat cerebellum. J Neurophysiol 81:277–287

Ekerot CF, Kano M (1989) Stimulation parameters influencing climbing fibre induced long-term depression of parallel fibre synapses. Neurosci Res 6:264–268

Gall D, Prestori F, Sola E et al (2005) Intracellular calcium regulation by burst discharge determines bidirectional longterm synaptic plasticity at the cerebellum input stage. J Neurosci 25:4813–4822

Hansel C, Linden DJ (2000) Long-term depression of the cerebellar climbing fiber-Purkinje neuron synapse. Neuron 26:473–482

Hansel C, Linden DJ, D'Angelo E (2001) Beyond parallel fiber LTD: the diversity of synaptic and nonsynaptic plasticity in the cerebellum. Nat Neurosci 4:467–475

Häusser M, Clark BA (1997) Tonic synaptic inhibition modulates neuronal output pattern and spatiotemporal synaptic integration. Neuron 19:665–678

Ito M, Sakurai M, Tongroach P (1982) Climbing fiber induced depression of both mossy fiber responsiveness and glutamate sensitivity of cerebellar Purkinje cells. J Physiol (Lond) 324:113–134

Kano M (1996) Long-lasting potentiation of GABAergic inhibitory synaptic transmission in cerebellar Purkinje cells: its properties and possible mechanisms. Behav Brain Sci 19:354–361

Kano M, Rexhausen U, Dreessen J et al (1992) Synaptic excitation produces a long-lasting rebound potentiation of inhibitory synaptic signals in cerebellar Purkinje cells. Nature 356:601–604

Kawaguchi S, Hirano T (2000) Suppression of inhibitory synaptic potentiation by presynaptic activity through postsynaptic GABAB receptors in a Purkinje neuron. Neuron 27:339–347

Linden DJ (1998) Synaptically-evoked glutamate transport currents may be used to detect the expression of long-term potentiation in cerebellar culture. J Neurophysiol 79:3151–3156

Lonart G, Schoch S, Kaeser PS et al (2003) Phosphorylation of RIM1alpha by PKA triggers presynaptic long-term potentiation at cerebellar parallel fiber synapses. Cell 115:49–60

Pugh JR, Raman IM (2006) Potentiation of mossy fiber EPSCs in the cerebellar nuclei by NMDA receptor activation followed by postinhibitory rebound current. Neuron 51:113–123

Safo PK, Regehr WG (2005) Endocannabinoids control the induction of cerebellar LTD. Neuron 48:647–659

Salin PA, Malenka RC, Nicoll RA (1996) cAMP mediates a presynaptic form of LTP at cerebellar parallel fiber synapses. Neuron 16:797–803

Shen Y, Linden DJ (2005) Long-term potentiation of neuronal glutamate transporters. Neuron 46:715–722

Shen Y, Hansel C, Linden DJ (2002) Glutamate release during LTD at cerebellar climbing fiber-Purkinje cell synapses. Nat Neurosci 5:725–726

Wang YT, Linden DJ (2000) Expression of cerebellar long-term depression requires postsynaptic clathrin-mediated endocytosis. Neuron 25:635–647

Wang DJ, Su LD, Wang YN et al (2014) Long-term potentiation at cerebellar parallel fiber-Purkinje cell synapses requires presynaptic and postsynaptic signaling cascades. J Neurosci 34:2355–2364