Chapter 22
Stellate Cells

Siqiong June Liu and Christophe J. Dubois

Abstract Stellate cells are inhibitory interneurons located in the molecular layer of the cerebellar cortex. Stellate cells receive excitatory inputs from parallel fibers (PF) and climbing fibers and suppress the activity of Purkinje cells through feed-forward inhibition in the cerebellar cortex. A variety of mechanisms regulate GABA release at inhibitory synapses in the cerebellar cortex cells and consequently motor tasks.

Keywords Inhibitory interneurons • Stellate cells • Synaptic plasticity • AMPA receptors • GABA release

22.1 Introduction

In vivo studies reveal that cerebellar interneurons are vitally important during behavioral tasks such as motor coordination because a selective increase in $GABA_A$ receptor activity in Purkinje cells causes deficits in motor coordination (Wulff et al. 2007) and mutations in Kv1.1 channels enhance GABA release from stellate cells, causing type 1 episodic ataxia (Herson et al. 2003). Genetic deletion of GABA receptors on Purkinje cells impairs the consolidation of vestibulo-cerebellar motor learning (Wulff et al. 2009), and thus inhibitory transmission is critical for motor learning. Associative learning in the cerebellum, such as fear conditioning (Scelfo et al. 2008), enhances GABA release and associative eye-blink conditioning reduces the activity of Purkinje cells. Given the importance of inhibitory transmission in cerebellar function, GABA release at inhibitory synapses in the cerebellum is closely regulated.

S.J. Liu (✉) • C.J. Dubois
Department of Cell Biology and Anatomy, Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA
e-mail: sliu@lsuhsc.edu

D.L. Gruol et al. (eds.), *Essentials of Cerebellum and Cerebellar Disorders*,
DOI 10.1007/978-3-319-24551-5_22

22.2 Stellate Cells and Synaptic Transmission

22.2.1 Excitatory Synaptic Transmission

Stellate cells are electrically compact and can be activated by a single excitatory input, triggering GABA release onto Purkinje cells. Because PFs also innervate Purkinje cells, feed-forward inhibition via stellate cells gives rise to a delayed inhibition and thereby restrict the excitation of Purkinje cells to the onset of excitatory input. Excitatory transmission at the PF to stellate cell synapse is mediated by postsynaptic AMPA receptors, which do not contain GluA2 subunits and are permeable to Ca^{2+}. Synaptic currents display rapid kinetics and an increased current amplitude when activated by two consecutive stimuli, allowing stellate cells to respond to high frequency excitatory inputs, such as occurs during sensory stimulation (Chadderton et al. 2004). Ca^{2+} entry via AMPA receptors triggers the release of endocannabinoids from stellate cells, which reduce glutamate release from PFs (Soler-Llavina and Sabatini 2006). Consequently this lowers the excitatory drive for feed-forward inhibition in the cerebellar circuit. Stimulation of climbing fiber also evokes excitatory synaptic response in stellate cells. Co-stimulation of these two excitatory inputs in vivo induces a lasting increase in EPSPs at the PF-stellate cell synapse, which is reversed by stimulation of PFs alone (Jörntell and Ekerot 2003). Thus stellate cells mediate associative learning-induced change.

Synaptic AMPA receptors in stellate cells undergo dynamic changes in response to presynaptic activity. Repetitive stimulation of PFs triggers a long lasting increase in synaptic GluA2 content, which replace GluA2-lacking AMPA receptors (Liu and Cull-Candy 2000) in stellate cells. This not only reduces the amplitude and prolongs the decay time of EPSCs, but also lowers the Ca^{2+}-permeability of AMPA receptors, producing a qualitative change in synaptic transmission. The switch is triggered by activation of synaptic AMPA or extrasynaptic NMDA receptors, and requires a Ca^{2+}-rise that activates PKC, leading to a PICK-dependent insertion of GluA2-containing receptors (Liu and Cull-Candy 2000; Sun and Liu 2007). Activation of mGluRs can also induce a switch in AMPA receptor subtypes via a mechanism that requires protein synthesis (Kelly et al. 2009). The switch in synaptic AMPA receptor phenotype reduces the ability of sensory stimulation to evoke multiple action potentials in stellate cells and thereby weakens the feed-forward inhibition.

Acute stress can also enhance gene transcription of GluA2 in stellate cells (Liu et al. 2010). Stress causes increased synaptic input to the cerebellum from norepinephrine containing fibers. Release of norepinephrine in the cerebellum activates β-adrenergic receptors and elevates cAMP levels. This increases Ca^{2+} entry during action potentials, activates ERK pathways and promotes GluA2 transcription in stellate cells. Consequently the elevated GluA2 expression prolongs the synaptic current duration and enhances the ability of each synaptic input to evoke an action potential and thus the feed-forward inhibition (Savtchouk and Liu 2011). Therefore acute stress can induce a lasting change in the activity and computation within the cerebellar circuitry.

22.2.2 Inhibitory Synaptic Transmission

Interneurons innervate each other to form inhibitory networks and provide the inhibitory inputs to Purkinje cells. Enhanced GABA release by the inhibitory interneurons is thought to promote synchronous activity of interneuron network and suppress Purkinje cell activity. Glutamate released from PFs and Purkinje cell dendrites enhance GABA release (Duguid and Smart 2004; Liu and Lachamp 2006), altering the balance between excitatory and inhibitory transmission. A train of PF stimulation triggers glutamate spillover which activates presynaptic NMDA receptors, inducing a lasting increase in GABA release via a mechanism that requires PKA and an active zone protein, RIM1α (Lachamp et al. 2009; Dubois et al. 2016). This alters the pattern and reduces the frequency of action potential firing in synaptically connected stellate cells. Neuromodulators, including noradrenaline (Liano and Gerschenfeld 1993) and neuropeptide Y (Dubois et al. 2012) also induce a sustained increase in GABA release. Such activity-dependent potentiation may underlie the associative learning-induced increase in GABA release.

22.2.3 Presynaptic Regulation

Endocannabinoids are critically involved in learning and extinction and dysregulation of endocannabinoid metabolism leads to cerebellar ataxia in PHARC disease (Fiskerstrand et al. 2010). In the cerebellar cortex depolarization of Purkinje cells triggers the release of endocannabinoids which activate the G-protein coupled CB1 receptors at the presynaptic terminal of interneurons (Yoshida et al. 2002; Beierlein and Regehr 2006). This decreases GABA release and reduces action potential firing in stellate cells (Kreitzer et al. 2002). The axons of interneurons extend over several hundred micrometers in a parasagittal plane and inhibit neighboring Purkinje cells, producing lateral inhibition. Thus inhibition of interneuron firing can lead to lateral excitation in the cerebellar cortex.

22.3 Gap Junctions

Interneurons are connected via gap junctions allowing current flow between neighboring cells. These electrical connections play a key role in temporal synchronization of neuronal activity (Mann-Metzer and Yarom 1999). Each stellate cells is directly connected to one neighboring interneurons in the sagittal plane (Alcami and Marty 2013). Thus changes in membrane potential could spread among the interneurons. The pattern of connections (Rieubland et al. 2014) contributes to the spatial convergence onto Purkinje cells where seven interneurons form functional synapses onto a single Purkinje cell (Kim et al. 2014). Therefore electrical networks

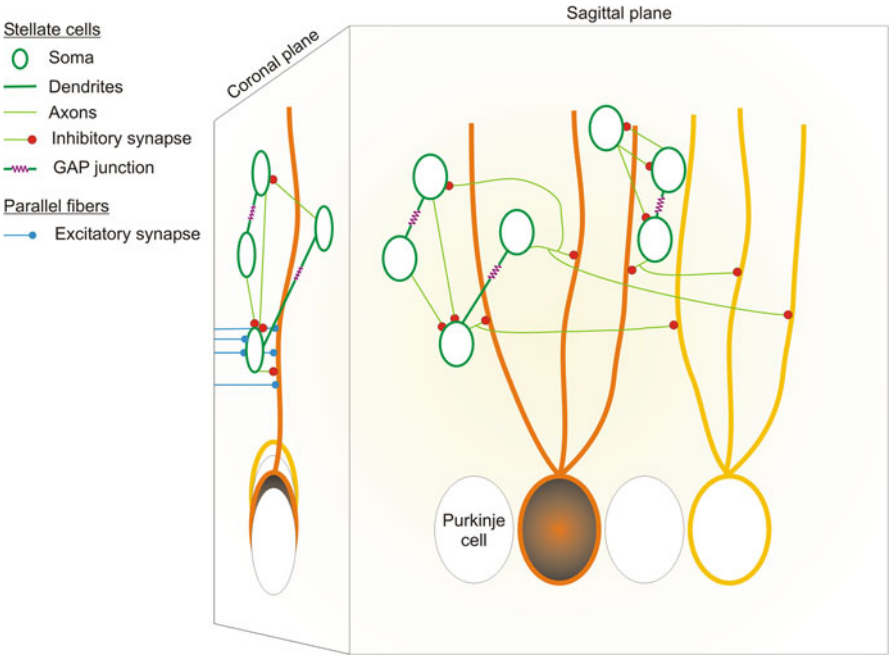

Fig. 22.1 Schematic of the connections made by molecular layer interneurons

spatially and temporally coordinate interneurons, which ultimately influence convergence of synaptic inhibition onto Purkinje cells, the only output neurons in the cerebellar cortex. In conclusion, both chemical and electrical synapses are critical in shaping the activity of Purkinje cells and controlling information processing in the cerebellum (Fig. 22.1).

References

Alcami P, Marty A (2013) Estimating functional connectivity in an electrically coupled interneuron network. PNAS 110:E4798–E4807

Beierlein M, Regehr WG (2006) Local interneurons regulate synaptic strength by retrograde release of endocannabinoids. J Neurosci 26:9935–9943

Chadderton P, Margrie TW, Häusser M (2004) Integration of quanta in cerebellar granule cells during sensory processing. Nature 428:856–860

Dubois C, Ramamoorthy P, Whim M, Liu S (2012) Activation of NPY type 5 receptors induces a long-lasting increase in spontaneous GABA release from cerebellar inhibitory interneurons. J Neurophysiol 107:1655–1665

Dubois CJ, Lachamp PM, Sun L, Mishina M, Liu SJ (2016) Presynaptic GluN2D receptors detect glutamate spillover and regulate cerebellar GABA release. J Neurophysiol 115:271–285

Duguid IC, Smart TG (2004) Retrograde activation of presynaptic NMDA receptors enhances GABA release at cerebellar interneuron-Purkinje cell synapses. Nat Neurosci 7:525–533

Fiskerstrand T et al (2010) Mutations in ABHD12 cause the neurodegenerative disease PHARC: an inborn error of endocannabinoid metabolism. Am J Hum Genet 87:410–417
Herson PS, Virk M, Rustay NR, Bond CT, Crabbe JC, Adelman JP, Maylie J (2003) A mouse model of episodic ataxia type-1. Nat Neurosci 6:378–383
Jörntell H, Ekerot C-F (2003) Receptive field plasticity profoundly alters the cutaneous parallel fiber synaptic input to cerebellar interneurons in vivo. J Neurosci 23:9620–9631
Kelly L, Farrant M, Cull-Candy SG (2009) Synaptic mGluR activation drives plasticity of calcium-permeable AMPA receptors. Nat Neurosci 12:593–601
Kim J, Lee S, Tsuda S, Zhang X, Asrican B, Gloss B, Feng G, Augustine GJ (2014) Optogenetic mapping of cerebellar inhibitory circuitry reveals spatially biased coordination of interneurons via electrical synapses. Cell Rep 7:1601–1613
Kreitzer AC, Carter AG, Regehr WG (2002) Inhibition of interneuron firing extends the spread of endocannabinoid signaling in the cerebellum. Neuron 34:787–796
Lachamp PM, Liu Y, Liu SJ (2009) Glutamatergic modulation of cerebellar interneuron activity is mediated by an enhancement of GABA release and requires protein kinase A/RIM1alpha signaling. J Neurosci 29:381–392
Liu S, Cull-Candy SG (2000) Synaptic activity at calcium-permeable AMPA receptors induces a switch in receptor subtype. Nature 405:454–458
Liu SJ, Lachamp P (2006) The activation of excitatory glutamate receptors evokes a long-lasting increase in the release of GABA from cerebellar stellate cells. J Neurosci 26:9332–9339
Liu Y, Formisano L, Savtchouk I, Takayasu Y, Szabó G, Zukin RS, Liu SJ (2010) A single fear-inducing stimulus induces a transcription-dependent switch in synaptic AMPAR phenotype. Nat Neurosci 13:223–231
Llano I, Gerschenfeld HM (1993) Beta-adrenergic enhancement of inhibitory synaptic activity in rat cerebellar stellate and Purkinje cells. J Physiol 468:201–224
Mann-Metzer P, Yarom Y (1999) Electrotonic coupling interacts with intrinsic properties to generate synchronized activity in cerebellar networks of inhibitory interneurons. J Neurosci 19:3298–3306
Rieubland S, Roth A, Häusser M (2014) Structured connectivity in cerebellar inhibitory networks. Neuron 81:913–929
Savtchouk I, Liu SJ (2011) Remodeling of synaptic AMPA receptor subtype alters the probability and pattern of action potential firing. J Neurosci 31:501–511
Scelfo B, Sacchetti B, Strata P (2008) Learning-related long-term potentiation of inhibitory synapses in the cerebellar cortex. PNAS 105:769–774
Soler-Llavina GJ, Sabatini BL (2006) Synapse-specific plasticity and compartmentalized signaling in cerebellar stellate cells. Nat Neurosci 9:798–806
Sun L, Liu SJ (2007) Activation of extrasynaptic NMDA receptors induces a PKC-dependent switch in AMPA receptor subtypes in mouse cerebellar stellate cells. J Physiol 583:537–553
Wulff P et al (2007) From synapse to behavior: rapid modulation of defined neuronal types with engineered GABAA receptors. Nat Neurosci 10:923–929
Wulff P et al (2009) Synaptic inhibition of Purkinje cells mediates consolidation of vestibulocerebellar motor learning. Nat Neurosci 12:1042–1049
Yoshida T, Hashimoto K, Zimmer A, Maejima T, Araishi K, Kano M (2002) The cannabinoid CB1 receptor mediates retrograde signals for depolarization-induced suppression of inhibition in cerebellar Purkinje cells. J Neurosci 22:1690–1697