Chapter 28
GABA Pathways and Receptors

Tomoo Hirano

Abstract GABAergic neurons including Purkinje cells play critical roles in cerebellar neuronal circuits. In the cerebellar cortex, molecular layer interneurons (stellate and basket cells) provide feedforward inhibitory loops between parallel fibers and Purkinje cells, and granular layer interneurons (Golgi cells) form feedback inhibition loops between granule cells. Some GABAergic neurons in the cerebellar nuclei inhibit inferior olive neurons, which send excitatory climbing fibers to the cerebellum. The cerebellar nuclear neurons and Purkinje cells are rare examples of GABAergic projection neurons. Cerebellar neurons express various types of ionotropic and metabotropic GABA receptors, which mediate the effects of GABA, and granule cells express extrasynaptic ionotropic GABA receptors that play a role in tonic inhibition. Both excitatory synapses on GABAergic neurons and GABAergic synapses show neuronal activity dependent plasticity, which contribute to motor learning. Several types of mutant mice defective in GABAergic neurons or synaptic functions have been found or generated, and they show failures in motor coordination and/or motor learning. Dysfunctions of cerebellar GABAergic system have been suggested to be causes of ataxia, and a GABA-mimetic drug improves motor coordination in some ataxic patients.

Keywords GABA • GABA_A receptor • GABA_B receptor • Purkinje cell • Stellate cell • Basket cell • Golgi dell

28.1 GABA Pathways in the Cerebellum

There are several types of GABAergic inhibitory neurons in the cerebellum (Fig. 28.1). Among them, Purkinje cells are sole output neurons of the cortex and send output to the deep cerebellar nuclei. Other GABAergic neurons are the interneurons, stellate, basket cells, and Golgi cells. Major inputs to the cerebellum are

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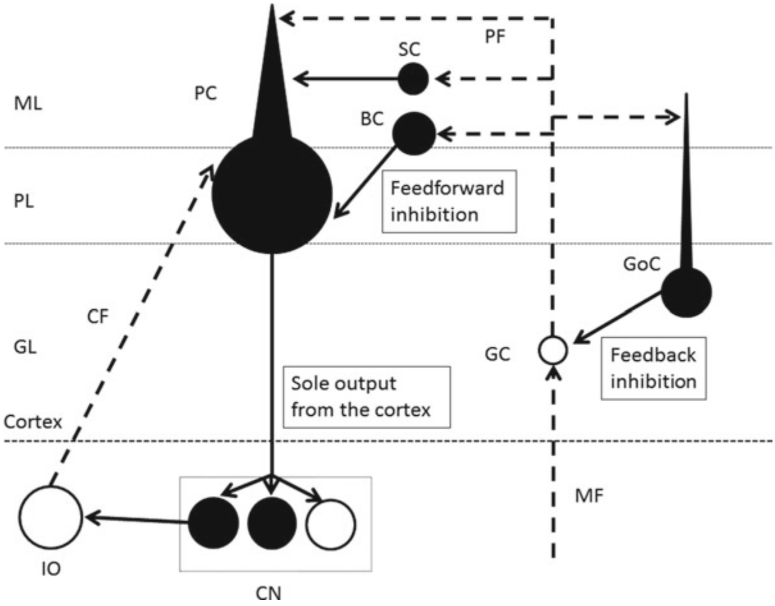

Fig. 28.1 Cerebellar neuronal circuits. *Filled* and *open* symbols represent GABAergic and glutamatergic neurons, respectively, and *solid* and *broken lines* indicate GABAergic and glutamatergic axons, respectively. *ML* molecular layer, *PL* Purkinje cell layer, *GL* granular layer, *IO* inferior olive nuclei, *CN* cerebellar nuclei, *CF* climbing fiber, *MF* mossy fiber, *PF* parallel fiber, *PC* Purkinje cell, *SC* stellate cell, *BC* basket cell, *GC* granule cell, *GoC* Golgi cell

glutamatergic and come through the excitatory mossy and climbing fibers. Mossy fibers form synapses on granule cells in the cortical granular layer and also on neurons in the cerebellar nuclei. A granule cell extends an axon to the molecular layer, where it forms a parallel fiber that sends excitatory glutamatergic output to Purkinje cells and also to two types of GABAergic interneurons, stellate and basket cells, which in turn send inhibitory output to Purkinje cells. A basket cell forms synapses on the axon hillocks of Purkinje cells and effectively suppresses action potential generation. On the other hand, a stellate cell forms synapses on dendrites of Purkinje cells and might selectively suppress the effect of nearby parallel fiber synapses. Stellate and basket cells form feed-forward inhibitory loops between parallel fibers and Purkinje cells. Golgi cells are located in the granular layer. They receive parallel fiber input and inhibit granule cells, thus forming an inhibitory feedback loop.

There are glutamatergic and GABAergic neurons in the deep cerebellar nuclei, and some of them are regulated by GABAergic output of Purkinje cells. One type of GABAergic nuclear neuron sends output to the inferior olive nuclei, which in turn send climbing fibers to the cerebellum. Purkinje cells and GABAergic nuclear neurons innervating the inferior olive are rare examples of inhibitory projection neurons in the central nervous system.

28.2 GABA Receptors in the Cerebellum

GABA receptors, which mediate the effects of GABA, are classified into ionotropic $GABA_A$ and $GABA_C$ receptors, and metabotropic $GABA_B$ receptors. An ionotropic GABA receptor is composed of five subunits. There are 19 genes for ionotropic GABA receptor subunits. They are α1-6, β1-3, γ1-3, δ, ε, θ, π, and three types of ρ subunits. ρ subunits form $GABA_C$ receptors, and others form $GABA_A$ receptors (Olsen and Sieghart 2009). The majority of $GABA_A$ receptors are composed of α, β and γ subunits. $GABA_A$ receptors consisting of different subunits contribute to differential effects of GABA in the cerebellum (Wisden et al. 1996). A Purkinje cell expresses α1, β2, β3 and γ2 subunits; basket and stellate cells express α1, β2 and γ2 subunits; a granule cell expresses α1, α6, β2, β3, γ2 and δ subunits. In a granule cell, α1, α6, β2 and γ2 subunits are found in synapses formed by a Golgi cell and also on extrasynaptic membrane at low levels. The δ-containing GABA receptors are found only on extrasynaptic membrane and show single channel currents with small conductance, long open time and little desensitization, contributing tonic inhibition of a granule cell (Olsen and Sieghart 2009).

The metabotropic $GABA_B$ receptors are hetero-dimers composed of $GABA_{B1}$ and $GABA_{B2}$, and coupled with Gi protein suppressing the activity of adenylyl cyclase. Both $GABA_{B1}$ and $GABA_{B2}$ show high level expression around glutamatergic synapses between parallel fibers and a Purkinje cell. Presynaptically, $GABA_B$ receptors are found on extrasynaptic membrane of parallel fibers, and postsynaptically both on postsynaptic and extrasynaptic membrane of a Purkinje cell (Lujan and Shigemoto 2006). These $GABA_B$ receptors around glutamatergic synapses seem to be activated by ambient GABA. Granule, basket, stellate and Golgi cells also express $GABA_B$ receptors.

28.3 Regulation of GABAergic Neurons and Synapses

Firing patterns of cerebellar GABAergic neurons are modulated by neuronal activities. Synaptic transmission between parallel fibers and a Purkinje cell undergoes long-term depression after coupled activation of parallel fibers and a climbing fiber. Long-term depression has been considered as a primary cellular mechanism for motor learning. Parallel fiber input to a stellate cell is also modulated by activities of parallel and climbing fibers (Dean et al. 2010).

GABAergic synapses in the cerebellum also show plasticity. Synaptic transmission between a stellate cell and a Purkinje cell undergoes short-term and long-term plasticity depending on neuronal activities (Hirano and Kawaguchi 2014). Among them, rebound potentiation is long-lasting potentiation of the GABAergic transmission. It is induced by the climbing fiber activity followed by the increase in intracellular Ca^{2+} concentration of a Purkinje cell. Both rebound potentiation at GABAergic synapses and long-term depression at excitatory synapses work to depress the activity of a Purkinje cell depending on the climbing fiber input, which suggests a possible cooperation of the two types of synaptic plasticity in the cortical information processing. Indeed, suppression of rebound potentiation affects motor learning (Tanaka et al. 2013). Synaptic plasticity has also been reported at GABAergic and glutamatergic synapses in the cerebellar nuclei, and GABAergic Purkinje cell output is involved in regulation of synaptic plasticity (Zeng and Raman 2010).

28.4 Mutant Mice Affected in GABAergic Neurons or GABA Receptors

There are some mutant mouse lines affected in GABAergic neurons or synapses in the cerebellum. Lurcher mice and Purkinje cell degeneration (PCD) mice lose most of Purkinje cells during development and show motor dis-coordination. A transgenic mouse line in which Golgi cells can be ablated at a desired timing was raised (Watanabe et al. 1998). Golgi-cell ablation induces severe motor dis-coordination followed by partial recovery, which is accompanied with suppressed NMDA-receptor mediated synaptic response in granule cells. This suppression of excitatory response seems to counteract the loss of GABAergic inhibition caused by Golgi cell ablation, and to contribute to the partial recovery of motor coordination.

Transgenic mouse lines in which GABAergic synaptic transmission onto Purkinje cells are depressed have also been generated. In one type, $GABA_A$ receptor $\gamma 2$ subunit was knocked out (Wulff et al. 2009). The mice show suppressed GABAergic synaptic response in a Purkinje cell and motor learning defects. However, they show apparently normal motor coordination. A previous study reported that acute suppression of GABAergic synaptic transmission by drug application causes severe motor dis-coordination (Wulff et al. 2007). Therefore, relatively mild effect of chronic suppression of GABAergic transmission might be ascribed to some compensatory mechanisms in the cerebellum.

28.5 GABA in Cerebellar Ataxia

As mice models with defects in GABAergic neurons or synapses show motor dis-coordination and/or motor learning failures, some dysfunction in the cerebellar GABAergic systems might be a cause of cerebellar ataxia in human patients. Indeed, some patients have auto-antibody against glutamate decarboxylase, an enzyme catalyzing production of GABA from glutamate (Vianello et al. 2003). The antibody suppresses GABA release from basket cells depressing inhibitory synaptic transmission to Purkinje cells. An agrypnia patient showing ataxia has auto-antibody against $GABA_B$ receptor, which might affect GABA systems in the cerebellum (Frisullo et al. 2007).

In a mouse model of episodic ataxia type 1, mutation of K^+ channel increases the frequency and amplitude of spontaneous GABAergic synaptic currents in a Purkinje cell, which might be a cause of episodic ataxia (Herson et al. 2003). On the other hand, GABA-mimetic drug gabapentin improves motor coordination in some spinocerebellar ataxia type 6 patients (Nakamura et al. 2009), suggesting that drug treatment to support GABA system is therapeutically effective in some ataxic patients.

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