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REVIEW

ACTIVITY-DEPENDENT PLASTICITY OF DEVELOPING CLIMBING FIBER–PURKINJE CELL SYNAPSES

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Abstract—Elimination of redundant synapses and strengthening of the surviving ones are crucial steps in the development of the nervous system. Both processes can be readily followed at the climbing fiber to Purkinje cell synapse in the cerebellum. Shortly after birth, around five equally strong climbing fiber synapses are established. Subsequently, one of these five synaptic connections starts to grow in size and synaptic strength, while the others degenerate and eventually disappear. Both the elimination of the redundant climbing fiber synapses and the strengthening of the surviving one depend on a combination of a genetically coded blueprint and synaptic activity. Recently, it has been shown that synaptic activity affects the synaptic strength of developing climbing fibers. Remarkably, the same pattern of paired activity of the presynaptic climbing fiber and the postsynaptic Purkinje cell resulted in strengthening of already "large" climbing fibers and weakening of already "weak" climbing fibers. In this review, we will integrate the current knowledge of synaptic plasticity of climbing fibers with that of other processes affecting climbing fiber development. © 2009 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: cerebellum, development, synapse elimination, axonal competition, synaptic plasticity, parallel fiber.

Contents

The cerebellum, being centrally located in both the sensory and the motor pathways of the brain, is essential for sensorimotor integration and motor learning (Ito, 2000; Hansel et al., 2001; Krakauer and Shadmehr, 2006). In the cerebellum, input from the sensory organs comes together with input from the sensory and motor cortex (Kleinfeld et al., 1999). Neuronal input reaches the cerebellar cortex via two distinct glutamatergic pathways: the mossy fibers, originating in the spinal cord and a number of areas of the brainstem including the pontine nuclei (Miskolczy, 1931; Angaut and Sotelo, 1975; Künzle, 1975; Gerrits et al., 1985), and the climbing fibers coming from the inferior olive (Szentágothai and Rajkovits, 1959; Eccles et al., 1966a; Konnerth et al., 1990). The sole output neurons of the cerebellar cortex are the GABAergic Purkinje cells which project to the vestibular and cerebellar nuclei (Ito et al., 1964; Chan-Palay et al., 1979). From the cerebellar nuclei, cerebellar output targets motor areas like the red nucleus, the reticular formation and the superior colliculus (Asanuma et al., 1983; May, 2005). The other main target is the cerebral cortex via cerebellar projections to the thalamus (Leiner et al., 1991; Thach et al., 1992; Middleton and Strick, 1997). The specific brain regions participating in the sensorimotor loops depend amongst others on the sensory modality involved. The routes involved in whisker control are illustrated as example in Fig. 1A.

The cerebellar cortex is organized in three layers (Addison, 1911). The granule layer is packed with small granule cells, which form the main targets for the mossy fibers. Granule cells have ascending axons that bifurcate in the molecular layer to form the parallel fibers. Between the granule and the molecular layer is a monolayer of large Purkinje cells (Purkinje, 1838). Purkinje cells have a large dendritic tree extending in the molecular layer (Golgi, 1886). The distal part of the dendritic tree is covered with spines, on which the parallel fiber inputs are located (Ramón y Cajal, 1911). Each Purkinje cell receives hundreds of thousands of parallel fiber inputs, in addition to synapses along the ascending branches of the granule cell axons (MacKay and Murphy, 1976; Bower and Woolston, 1983; Napper and Harvey, 1988). The proximal part of the Purkinje cell dendritic tree is smooth and largely covered by the terminal of a single climbing fiber (Ramón y Cajal, 1911). The climbing fiber–Purkinje cell synapse forms an extremely strong connection, involving numerous contact sites. Finally, the Purkinje cells receive inhibitory input from two types of interneurons: the stellate and basket cells (Fig. 1B; Andersen et al., 1964; Eccles et al., 1966b) and

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Abbreviations: E, embryonic day; EPSC, excitatory postsynaptic current; GluRδ2, glutamate receptor type δ2; LTD, long-term depression; LTP, long-term potentiation; mGluR1, metabotropic glutamate receptor type 1; P, postnatal day; TrkB, tyrosine kinase B.

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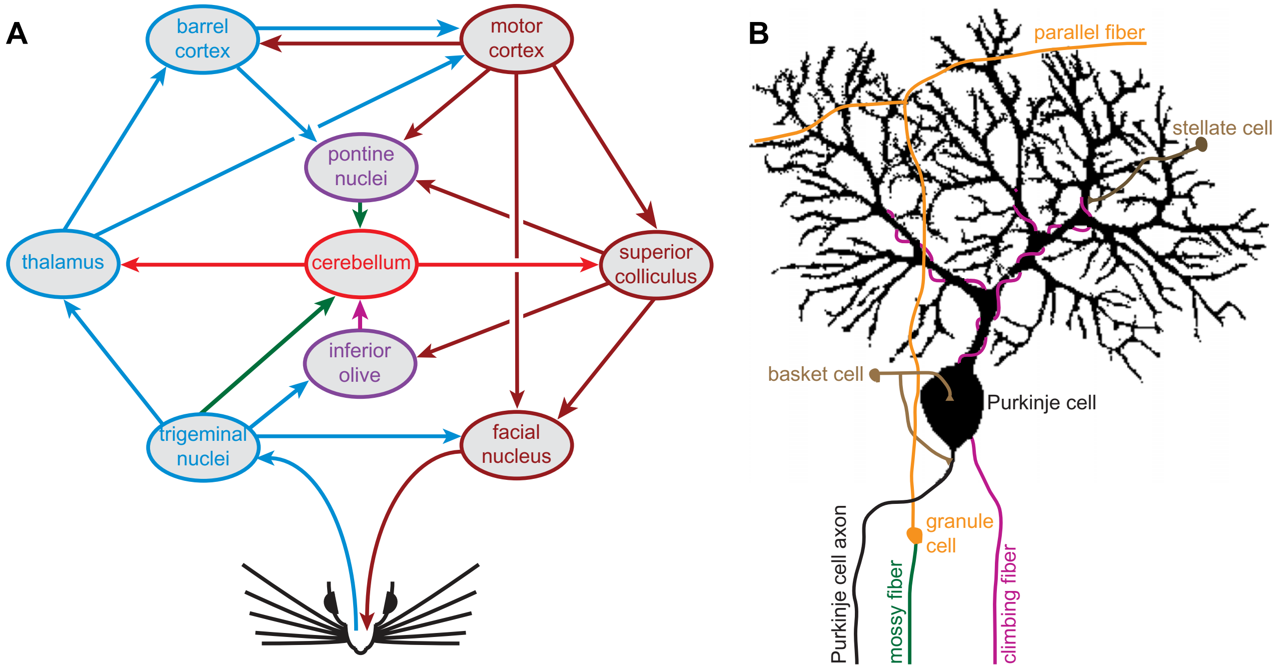

Fig. 1. The cerebellum is centrally involved in sensory and motor pathways. (A) Neuronal circuitry involved in the integration of tactile input from the whiskers and the coordination of whisker movement (cf. Kleinfeld et al. (1999) and references cited therein). (B) Purkinje cells are the sole output neurons of the cerebellar cortex. They are innervated by two types of inhibitory interneurons, the stellate and the basket cells and by two types of excitatory afferents, the climbing fibers originating from the inferior olive and by the axons of the cerebellar granule cells, which form the ascending branches and the parallel fibers. Climbing fibers innervate the smooth, proximal part of the Purkinje cell dendritic tree while the parallel fibers make synapses with the spines on the distal part of the Purkinje cell dendritic tree. Granule cells are in turn activated by mossy fibers.

probably also from neighboring Purkinje cells via axon collaterals (Chan-Palay, 1971; King and Bishop, 1982).

In this review, we will discuss the development of the climbing fiber–Purkinje cell synapses. We will relate this to different stages of the anatomical development of the cerebellar cortex and to the functional development of the other synaptic inputs to the Purkinje cells.

ANATOMICAL DEVELOPMENT OF THE CEREBELLUM

The cerebellum develops from the hindbrain, where it starts as a separate region at embryonic day 9 (E9) in mice (Zervas et al., 2004). It first becomes visible as a protrusion of the dorsal border of the fourth ventricle around E13 (Altman and Bayer, 1978). By that time, the Purkinje cells have already been formed (Miale and Sidman, 1961; Sillitoe and Joyner, 2007). The Purkinje cells, which are not larger than the other cells at that time (E13), migrate to form a multilayer below the molecular layer (Addison, 1911; Miale and Sidman, 1961). One should note that the time points mentioned here are indicative for the development in mice and rats, although regional variations exist as well as variations between individual strains. Around postnatal day 3 (P3), the developing Purkinje cells start to grow (Addison, 1911; Andrew, 1936). In the meantime, the Purkinje cells line up in a monolayer. This process depends on the extracellular matrix protein reelin (Rice and Curran, 2001) and is almost completed at P5 (Addison, 1911; Altman, 1972b). At that time, Purkinje cells still lack an apical dendrite, but they do develop a number of somatic protrusions (Altman, 1972b). Around P6, the apical dendrite starts to grow and the somatic protrusions gradually disappear (Fig. 2A; Altman, 1972b; McKay and Turner, 2005; Bosman et al., 2008). The dendritic tree reaches its maximal size only 2 to 3 months after birth (McKay and Turner, 2005).

Simultaneous with the development of the Purkinje cells, the afferent fibers grow out. Axons from neurons in the inferior olive reach the primitive cerebellum around E18 (Chédotal and Sotelo, 1992; Wassef et al., 1992). Subsequently they ramify and give rise to both thick and thin collaterals (Sugihara et al., 1999). The thick collaterals, the "climbing fibers," creep between the Purkinje cells ("creeper stage"), which have by that time just completed their migration phase and are organized in a multilayer (Chédotal and Sotelo, 1993; Sugihara, 2005). By P3, the first synaptic contacts between the climbing fibers and the somata of Purkinje cells are established (Fig. 2B; Crepel, 1971; Woodward et al., 1971; Altman, 1972b). With the outgrowth of the somatic protrusions of the Purkinje cells, these become also covered with climbing fiber synapses (Altman, 1972b).

Initially, each olivocerebellar axon forms around 100 "creeper" climbing fibers (Sugihara, 2005). Of these 100 ramifications, only around 10 develop a nest-like structure around a postsynaptic Purkinje cell soma ("nest stage") (Ramón y Cajal, 1911; O'Leary et al., 1971; Mason et al., 1990; Sugihara, 2005). The "creeper" climbing fibers that do not manage to form a "nest" become atrophic and