Neuroscience and Biobehavioral Reviews 36 (2012) 1153–1162

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

The role of calcium in synaptic plasticity and motor learning in the cerebellar cortex

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ARTICLE INFO

Article history:
Received 27 June 2011
Received in revised form 13 January 2012
Accepted 20 January 2012

Keywords:
Basket cells
Calcium
Cerebellum
Climbing fiber
Golgi cells
Granule cells
LTD
LTP
Mossy fibers
Motor learning
Parallel fibers
Purkinje cells
Synaptic plasticity
Stellate cells

ABSTRACT

The cerebellum is important for motor coordination, as well as motor learning and memories. Learning is believed to occur in the cerebellar cortex, in the form of synaptic plasticity. Central to motor learning theory are Purkinje cells (PCs), which are the sole output neurons of the cerebellar cortex. Motor memories are postulated to be stored in the form of long-term depression (LTD) at parallel fiber synapses with PCs, once thought to be the only plastic synapse in the cerebellar cortex. However, in the past few decades many studies have demonstrated that several other synapses in the cerebellar cortex are indeed plastic, and that LTD or long-term potentiation at these various synapses could affect the overall output signal of PCs from the cerebellar cortex. Almost all of these forms of synaptic plasticity are dependent on calcium to some extent. In the current review we discuss various types of synaptic plasticity in the cerebellar cortex and the role of calcium in these forms of plasticity.

Contents

1. Introduction 1153
2. Basic circuit in the cerebellar cortex 1154
3. The role of calcium in cell signaling 1155
4. Signaling and plasticity at synapses in the cerebellar cortex 1155
   4.1. Purkinje cells 1155
   4.2. Mossy fiber inputs 1157
   4.3. Golgi cells 1158
   4.4. Interneurons 1159
5. Insights from transgenic mouse models 1159
6. Summary and concluding remarks 1160
   Acknowledgments 1160
   References 1160

1. Introduction

The cerebellum, which is Latin for "little brain", lies posterior to the pons and medulla oblongata and inferior to the occipital lobes of the cerebral hemispheres. Cerebellar damage often leads to symptoms such as ataxia, asynergy, dysmetria, and motor learning deficits in humans (Schmahmann, 2004; Stoodley and

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0149-7634/$ – see front matter.
doi:10.1016/j.neubiorev.2012.01.005

Schmahmann, 2010) as well as in animals (Lalonde and Strazielle, 2001; Rinaldo and Hansel, 2010). Therefore, the ability to modulate motor commands and fine-tune complex movements has largely been attributed to the cerebellum. Recent evidence suggests that the cerebellum may have cognitive functions and play a role in the processing of emotions (Strick et al., 2009). In addition, the cerebellum has received considerable attention because of its proposed role in motor learning behavior (Ito, 2006). Central to motor learning theories are Purkinje cells (PCs) of the cerebellar cortex. PCs are important because they represent the only output cell of the cerebellar cortex and as such, play a vital role in normal cerebellar function, i.e. motor coordination. In addition to motor coordination, PCs are postulated to play a major role in certain forms of motor learning, including associative eyeblink conditioning and adaptation of the vestibulo-ocular reflex (Schmolesky et al., 2002). Synaptic plasticity in PCs has long been postulated to represent the underlying cellular changes that lead to motor memories. Long term depression (LTD) at parallel fiber (PF)-PC synapses in particular remains a widely accepted vertebrate model for the cellular mechanism that underlies synaptic changes during motor learning and memories in the cerebellum, and several molecular components have been identified which appear to be necessary for its induction, including glutamate receptors and various kinases (Massey and Bashir, 2007). It was long thought that PF-PC synapses were the only synapses capable of plasticity in the cerebellar cortex, however in recent years plasticity has been described at several other synapses in the cortex (Hansel et al., 2001; Dean et al., 2010). In this review, we provide a brief overview of the types of synaptic plasticity present in the cerebellar cortex, with a particular emphasis on the role of calcium in those synaptic changes.

2. Basic circuit in the cerebellar cortex

The cell bodies of PCs are found in a specific layer of the cerebellar cortex appropriately named, the PC layer. The dendrites of PCs project into the molecular layer of the cortex, while the axons of PCs pass through the granule cell (GC) layer and project out of the cerebellar cortex (see Fig. 1). PCs receive two types of excitatory synaptic inputs. The first is from climbing fibers (CFs), which arise from the inferior olive (IO) of the brain stem and carry sensory, and perhaps motor information required for learning (Dean et al., 2010; Ito, 2006). The second excitatory input to PCs is from numerous PFs, which are bifurcations of the axons of GCs that run along the long axis of the folia in the molecular layer of the cerebellar cortex. The dendrites of GCs receive their afferent projections from mossy fibers (MFs), which are also excitatory and carry sensory information to the cerebellum from precerebellar nuclei such as the pontine and vestibular nuclei (Eccles et al., 1966).

Multiple CFs innervate PCs during development, however PCs receive input from only a single CF in adulthood, which represents approximately 1500 CF-PC synaptic contacts (Strata and Rossi, 1998). These contacts are considered to be strong excitatory synapses, in that there is a high probability of neurotransmitter release when the CF is stimulated (Dittman and Regehr, 1998), which in turn leads to a response in PCs. These CFs primarily contact the more proximal portions of the PC dendritic arbor, while

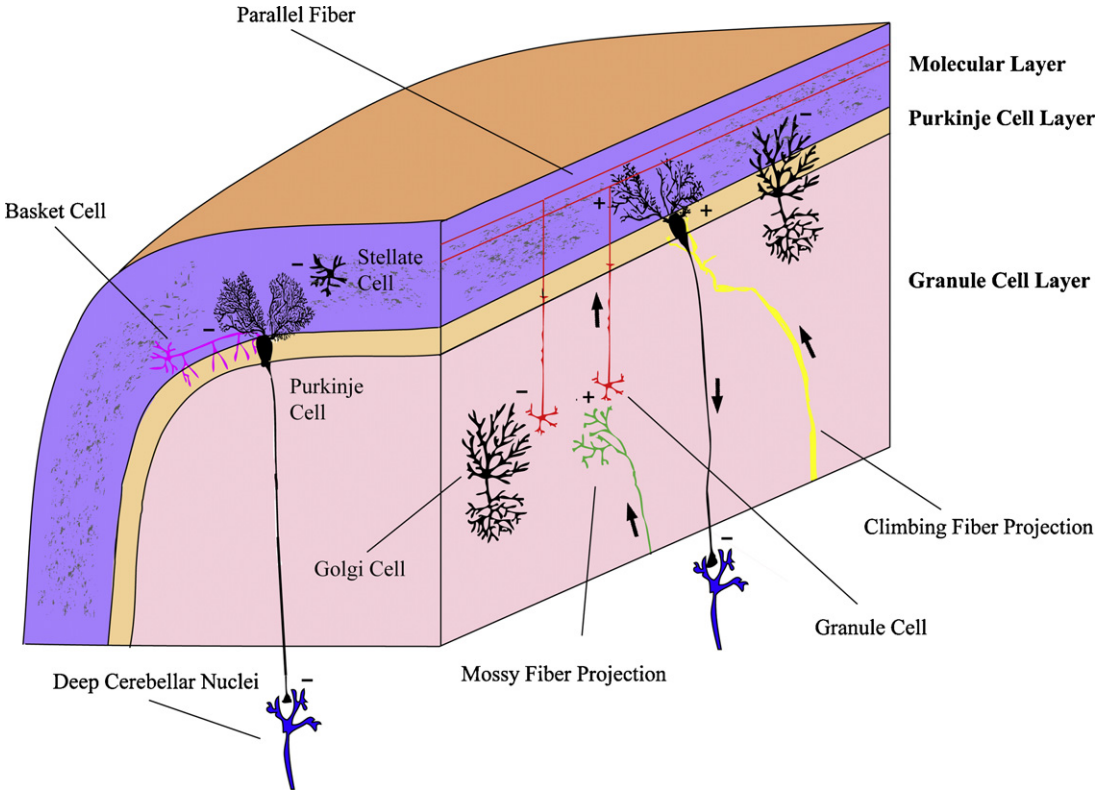

Fig. 1. Neurons and circuits of the cerebellum. The main signaling circuit of the cerebellum begins with an incoming stimulus from the mossy fiber (MF; green), a projection from precerebellar nuclei (e.g. vestibular nuclei, reticular nuclei). The MF forms an excitatory synapse with granule cells (GCs; red) that is also modulated by Golgi cell (GoC; black) inhibitory input. When excited, the GCs stimulate Purkinje cells (PCs; black) via the GC projections called parallel fibers (red), which can also be inhibited by neighboring GoCs. However, the excitability of PCs is further modulated by several other types of cells. The inhibitory interneurons (basket and stellate cells, magenta/black, respectively) are located in the molecular layer and provide inhibitory input. PCs receive additional excitatory input from climbing fibers (yellow), which originate in the inferior olivary complex. Based on the temporal and spatial summation of all incoming signals, the PCs will either continue their tonic inhibition of the deep cerebellar nuclei (blue) or the inhibition will be temporarily attenuated; generally this is either a result of, or will modulate, motor behavior and/or motor learning based in the cerebellum. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)