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NEW INSIGHTS IN CEREBELLAR FUNCTION

P. STRATA,[a,b]* W. T. THACH[c] AND O. P. OTTERSEN[d]

[a]*EBRI-Santa Lucia Foundation (IRCCS), Via del Fosso di Fiorano 64, 00143 Rome, Italy*

[b]*Department of Neuroscience and National Institute of Neuroscience–Italy, University of Turin, Corso Raffaello 30, 10125 Turin, Italy*

[c]*Departments of Anatomy and Neurobiology, Neurology, and Physical Therapy, Washington University School of Medicine, Box 8108, 660 South Euclid Avenue, St Louis, MO 63110, USA*

[d]*Centre for Molecular Biology and Neuroscience, Institute of Basic Medical Sciences, University of Oslo, POB 1105 Blindern, N-0317 Oslo, Norway*

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This volume is unique in providing a comprehensive and updated survey dedicated entirely and solely to the cerebellum. It contains papers that are in part reviews and in part original experimental work, emphasizing recent advances. The scope ranges widely from its molecular organization through to its roles in cognition: it bridges these different levels of interest and investigation.

The first paper summarizes the history of cerebellar functions from when function was inferred mainly from anatomy to relative recent times. It reports those principles of its structure and function that are well understood and met a wide general agreement (Glickstein et al., 2009).

The remaining papers deal with more recent and controversial aspects in order to provide an overview of the trends and to attempt to identify the directions and challenges of future research. Some describe how cerebellar cortex wiring is made and maintained while others delve into mechanisms of its functions and dysfunctions.

The well-described stereotyped architecture of the cerebellar cortex (Eccles et al., 1967; Palay and Chan-Palay, 1974) allows establishment of general principles that may subserve the development and maintenance of all neuronal wiring systems. The paper by Dipietrantonio and Dymecki (2009) presents findings on the implication of the transcription factor Zic1 as molecular determinant of mossy fiber (MF) cell body position within the brain stem. The MF nuclei located in the brainstem provide major cerebellar afferents to granule cells of the cerebellar cortex and output neurons of the cerebellar nuclei via a stereotyped ratio of crossed (contralaterally-directed) and uncrossed (ipsilaterally-directed) axon pathways with respect to the brainstem midline. They show that by increasing or reducing Zic1 levels the distribution of MF nuclei is shifted in the brainstem such as the proportion of the axon projecting to the ipsilateral cerebellum. Thus, they reveal a new role for Zic1 as a cell-autonomous regulator of key aspects of nucleus formation and axon pathway choice in the ventral brain stem. The paper by Sillitoe et al. (2009) focuses on the topographic distribution of the purkinje cells (PCs) and their axons that can be defined with respect to two coordinate systems; one based on the pattern of lobules and the other on PC gene expression in parasagittal clusters in the embryo (e.g. PC protein 2, Pcp2) and stripes in the adult (Voogd, 1989; e.g. ZebrinII). Since the relationship between the embryonic clusters of molecularly defined PCs and particular adult PC stripes is not clear they analyze the embryonic origins of ZebrinII parasagittal stripes (Brochu et al., 1990) following them from embryonic day 15 until adulthood.

Due to its peculiar disposition and conformation, the PC is an extraordinary model to identify intrinsic versus extrinsic factors influencing the acquisition of the mature dendritic tree. The paper by Sotelo and Dusart (2009) leads to the conclusion that the intensive remodeling of the PC dendritic tree that occurs in the early phase of the differentiation is mainly controlled by intrinsic factors whereas the second phase, required for the formation of their ultimate dendritic tree, depends both on intrinsic factors and interactions with afferent fibers.

The two main excitatory inputs to the cerebellar cortex, the climbing fiber (CF) and the parallel fiber (PF), project to two separate dendritic regions of the PC. How are they developing and maintained? The one-to-one relationship between the CF and the PC is reminiscent of the neuromuscular junction. Both systems initially have several projecting neurons contacting one target element, but over time and activity, the stronger synapses prevail and the weaker ones are eliminated (Crepel, 1982). In the cerebellar cortex the CF input is the first to develop at the time of birth while the PF synapses form a few days later. Whether CF dropout is determined in part or totally by the maturation of the PFs is discussed in several papers (Scelfo and Strata, 2005; Hashimoto et al., 2009; Bosman and Konnerth, 2009).

CF activity plays a basic role in shaping the architectural wiring of the cerebellar cortex. In addition to its phasic excitatory action, such an activity exerts a tonic inhibition on the firing of the PCs (Montarolo et al., 1982). This inhibition, initially assumed to be due to CF collaterals to inhibitory interneurons, has now been attributed to a spillover effect of glutamate released by the CFs (Szapiro and Barbour, 2009). In the latter paper there is also an account

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*Corresponding author. Tel: +39-011-6708175; fax:+39-011-6708174.
E-mail address: piergiorgio.strata@unito.it (P. Strata).
Abbreviations: CF, climbing fiber; LTD, long-term depression; LTP, long-term potentiation; MF, mossy fiber; PC, purkinje cell; PF, parallel fiber.

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of this parasynaptic transmission in the brain and the way multiple signaling pathways might avoid interactions.

CF activity is also important for the ongoing competition with the PFs and with GABAergic inputs. Lack of activity is followed by an intense spinogenesis in the proximal dendritic domain of the PCs and these spines are mainly innervated by the PFs. Thus, spines appear to be an intrinsic PC property whose distribution is controlled by the CF activity (Cesa and Strata, 2009; Sotelo and Dusart, 2009). CFs need to be active to maintain their own dendritic territory and to displace competitor afferents. The crucial role of the glutamate receptor $\delta 2$ subunit and cerebellin1 (Cbl1) in the cerebellar wiring is also discussed (Yuzaki, 2009; Mandolesi et al., 2009a,b). Additional features of the CF function are discussed below (Rokni and Yarom, 2009; Llinás, 2009).

Firing of PCs seems to be in part intrinsic and in part driven under the influence of excitatory and inhibitory inputs. In this context, several papers present an updated display of the neurotransmitters and modulators of synaptic activity in the cerebellar cortex. The ancillary AMPAR subunits—the so-called TARPs—play a vital role in influencing the variety of postsynaptic signaling in the CNS. TARP was first discovered in studying mutant mice with impaired granule cell transmission due to a lack of this subunit. A description of the important functional properties of TARPs present throughout the cerebellar neurons and glia is here presented by Coombs and Cull-Candy (2009).

Reference maps of the localization of the astounding number (22) of classic neuropeptides so far identified in the cerebellum are reviewed by Ito (2009); in addition, the functional role of some of them is highlighted. Corticotropin releasing factor (CRF) appears to be a major actor in the neuroendocrine cerebellum, as it is contained in CFs and its spontaneous release is required for the induction of cerebellar long-term depression (LTD). New data on the neuroendocrine components of the cerebellar cortex, and particularly the unipolar brush cells, are presented by Nunzi and Mugnaini (2009); their results invite further investigations on the additional class of peptides generated endoproteolytically by members of the granin family.

The role of intracellular Ca^{2+} induced through voltage-gated calcium channels has received much attention in cerebellar physiology. Here, an interesting mechanism of Ca^{2+} influx in PCs is described by Shin et al. (2009). Such an influx triggers the fusion of glutamate-containing vesicles in the somatodendritic region. The released glutamate could then activate mGluR1 on the same PC in an autocrine fashion to produce depolarization-induced slow current or diffuse in a retrograde manner to ligate interneuronal NMDA receptors thereby triggering depolarization-induced potentiation of inhibition.

The recently described bi-stability of Purkinje cells and the state-dependence of the complex spike waveform suggest that calcium currents may also play a pivotal role in both the complex spike waveform and the state of the membrane voltage (Rokni and Yarom, 2009). By using Ca^{2+} imaging to record the changes in intracellular Ca^{2+} that are elicited by either spontaneous or CF-evoked activity it has been shown that a continuous somatic Ca^{2+} influx occurs and determines the state firing of the PC. The state-dependence of these signals may have an impact both on intrinsic firing of Purkinje cells and on synaptic plasticity. Birnstiel et al. (2009) analyze the mechanisms for calcium transients in the unipolar brush cells; moreover, they review the intrinsic membrane properties that may shape the synaptic responses of this intriguing cell class, whose enrichment in the vestibulocerebellum supports their important role in cerebellar processing of vestibular inputs.

Although the role of cerebellum in motor learning has been widely investigated for a long time, this topic is still controversial regarding several aspects and in particular the location and the nature of the memory trace. In the original proposal outlined and developed by Marr (1969), Albus (1971) and Ito (1982; see Glickstein et al., 2009), LTD at the PF to PC synapses was assumed to be the basic mechanism of learning. Such a depression occurs by conjunctive stimulation of the PFs and of the CFs (Ito, 2001). However, depending on the pattern of electrical stimulation, several forms of long-term potentiation (LTP) of presynaptic or postsynaptic nature have also been described *in vitro* by stimulation of the PFs in isolation. The role of these LTPs in learning is still debated. Wang et al. (2009) have applied a high frequency stimulation of the PFs *in vivo* and by optical imaging they describe a long-term increase in response to PF stimulation that is postsynaptic in nature and is mGluR1-dependent. A behaviorally induced LTP of PF to PC synapses is described by Sacchetti et al. (2009) in association with cued fear learning. In this paper the authors review a series of experiments aimed at showing plastic changes within cerebellar vermal cortex for the regulation of autonomic and somatomotor acquired responses associated with emotion. A support to this hypothesis comes from human experiments revealing a different activation patterns in the cerebellar regions during pain perception and during learning sensory cues that anticipate pain experience (Ploghaus et al., 1999).

Using novel and different genetic techniques, Nakanishi (2009) selectively blocked different local circuits in the cerebellar network in order to study their implication in distinct cerebellum-dependent processes. By means of the reversible neurotransmission blocking (RNB) granule cell transmission to PCs was selectively and reversibly blocked in the cerebellar circuitry and it has been shown that PCs are essential for expression of conditioned eye-blink motor learning but that this memory is acquired and stored in deep cerebellar nuclei. In this same paper further contributions come from immunotoxin-mediated ablation of Golgi cells and from gene targeting of mGluR2.

The paper by Thompson and Steinmetz (2009) presents a detailed review summarizing a series of investigation performed on eye blink conditioning by using anatomical data, neuronal unit recordings, electrical stimulation, lesions and methods of reversible inactivation. The unconditioned stimulus (US) pathway involves activation of the inferior olive and its CF projects to the cerebellar cortex

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