Review

The modular architecture and neurochemical patterns in the cerebellar cortex

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ABSTRACT

The review deals with topical issues of the neuronal arrangement underlying basic cerebellar functions. The cerebellum and its auxiliary structures contain several hundreds of modules (so called "microzones"). Each module receives the corticopetal input specific for the lobule it belongs to and forms the topographic projection. The precision of the major input-output signal flow in the cerebellar cortex is provided by a pronounced stratification of its synaptic zones of a various origin and regular topography of its afferent connections, interneurons, and efferent neurons. There is a nice match between the anatomical and functional coordinates of the modules, whose spatial boundaries are determined by the spread of afferent excitation and local interneuron connections. The dynamic characteristics of the modules are analyzed by the example of the formation of the nitrergic neuron ensembles and cerebellar projections of corticopetal fibers. The authors discuss the cerebellar blood flow and its relation to the activity of NO/GABAergic Lugaro cells and other interneurons in the cerebellar cortex. A generalized scheme of intra- and intermodular communication is proposed.

1. Introduction

Since the first studies on the cerebellar cortex, scientists have been seeking for the basic principles underlying its complex structure to build realistic functional models (Braitenberg et al., 1997; Ito, 2006; Cerminara et al., 2013). Studying the neuronal diversity of the cerebellum is an important prerequisite for any further research on the subject. In particular, it is the cornerstone of the present-day cerebellar histophysiology.

The elements forming the cerebellar cortex are of three general types: a) mossy, climbing, serotonin-, and other monoaminergic fibers providing excitatory corticopetal inputs; b) axons of Purkinje cells forming inhibitory corticofugal projections; c) local (intracortical) connections of excitatory and inhibitory interneurons: basket, stellate, Golgi, Lugaro, candelabrum, granule, and unipolar brush cells (Fig. 1) (Palay, Chan-Palay, 1974; Kalinichenko, Motavkin, 2005; Ambrosi et al., 2007). Both these cells and fibers are oriented in different directions relative to the cortical plane.

Parallel fibers and axons of Lugaro cells run along the long axis of the cerebellar gyri (in transverse sections), while axons of other neuron types as well as climbing and mossy fibers lie in the sagittal plane of the gyri (Dieudonné, 2001; Sugihara et al., 2001).

To date, there is no widely accepted definition of corticocerebellar module (hereafter, cerebellar module). Usually, it is defined to be a regular (periodic) structure within the cerebellar cortex. Some authors consider it as an anatomically discrete termination zone of corticopetal afferents (Voogd, Glickstein, 1998) or associate with folia (cortical folds) (Welker, 1990), while others, as a system of connections between Purkinje cells and local circuit neurons (Bower, 2002) or a part of larger reciprocal connection systems integrating the cerebellar cortex, deep cerebellar nuclei, and brainstem nuclei (Ito, 2006). These approaches do not contradict one another, but reflect the current views on the structural and functional organization of the cerebellar cortex at different integration levels. Besides, to date, a large amount of data has been obtained on neurochemical compartments formed by neurons of a similar neurotransmitter profile. These compartments may comprise a separate level in the modular architectonics of the cerebellum.

Here, under cerebellar module we mean a regular microzone of the cerebellar cortex comprising certain afferents, their cortical targets, local connections, and efferent projections. This standpoint allows one to analyze classical and modern views on the structure, function, and connections of the cerebellar cortex. We critically revise the current
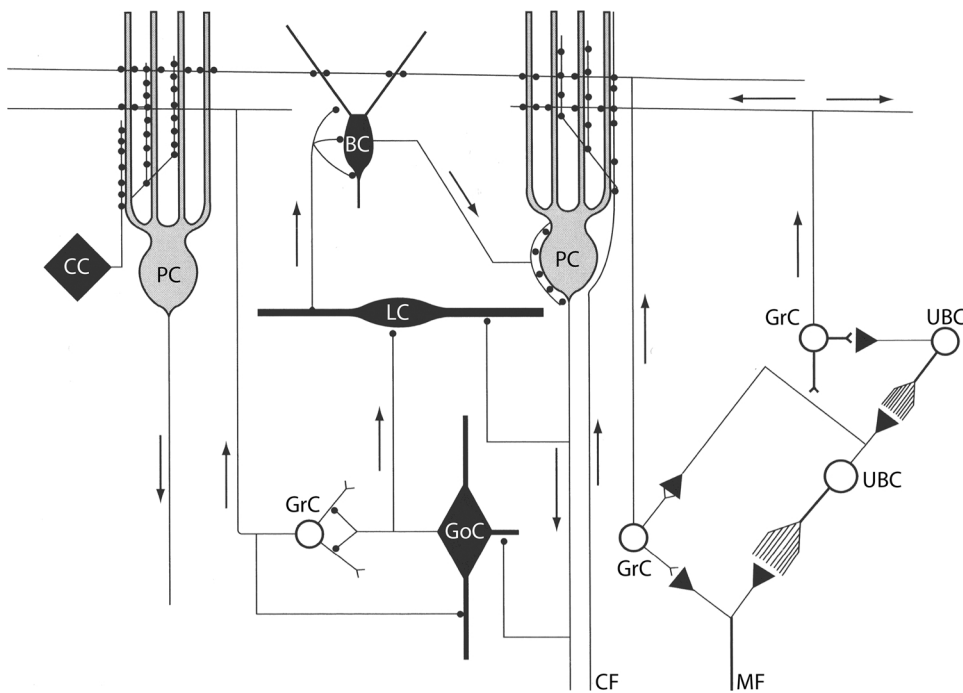
Fig. 1. Interneuron connections in a cerebellar module. GoC, Golgi cell; BC, basket cell; GrC, granule cells; CC, candelabrum cell; LC, Lugaro cell; PC, Purkinje cells; UBC, unipolar brush cells; CF, climbing fiber; MF, mossy fiber. Inhibitory GABA-ergic interneurons are black, and excitatory glutamatergic interneurons are white. Inhibitory Purkinje cells are gray. The arrows show the direction of signal transmission.

concepts of modular arrangement of the cerebellar cortex with an emphasis on neurotransmitter heterogeneity of its neurons and intracerebellar connections. We consider nitroxidergic (NO-ergic) interneurons as principal agents mediating intramodular integration and regulating local blood flow. The majority of facts and mechanisms reviewed come from research on chicken, rabbit, rat, monkey, mouse, and human. The present review is potentially useful for neuroscientists specializing in cerebellar anatomy, physiology, neurochemistry, architectonics, and vascularization.

2. Modular architectonics of the cerebellar cortex

Ramon y Cajal found (Ramon y Cajal, 1911) recurrent interneuronal collaterals, and Lorente de Nó formulated (Lorente de Nó, 1933) the law of multiplicity and reciprocity of interneuron connections. According to him, the cardinal element of any nerve center is a reverberatory circuit of reciprocal interneuronal connections. This model considers a local neural circuit with a presynaptic fiber terminating on a relay neuron. The relay neuron sends an axon collateral to a local short-axon interneuron that, in turn, contacts the relay neuron. This model resulted in the first rational explanation of integrative functions of the CNS and was confirmed by the discovery of local inhibitory interneurons, as well as feed-forward and feed-back inhibition in the cerebellar cortex (Eccles et al., 1967). Based upon this model, J. Szentágothai divided the gray matter into functionally independent fragments (local interneuron circuits) (Szentágothai, 1967). D. Hebb defined them as "cell ensembles" providing basic interneuron integration (Hebb, 1949). M. Scheibel and A. Scheibel introduced the term "module" for an elementary structural and functional unit within a nervous center (Scheibel and Scheibel, 1958).

The formulation of the module theory advanced our understanding of the CNS anatomy and cell composition. Its main theses are as follows: 1. Large brain structures known as nuclei and cortical formations are formed by repeating identical structural and functional units (modules). 2. Each module is a local neuron circuit transmitting and processing information in accordance with the circuit's properties and external connections. 3. There are numerous selective and specific intermodular connections 4. Groups of densely interconnected modules in different and often distantly located structures form a reciprocal communication network.

Each module forms local connections, whose anatomical boundaries are sometimes vague. Occasionally, they are surrounded by glial cells forming glomeruli. Module boundaries may coincide with those between afferent or efferent fibers. They may also coincide with microcirculatory vessels providing blood supply to the modules.

The cerebellar cortex is a tightly folded layer of the grey matter. Each ridge, so-called folium, contains the same set of highly ordered neurons. These form functional units (modules) processing multimodal afferent signals (Fig. 1). Granule cells comprise the bulk of the cerebellar neurons. Their axons travel to the molecular layer to form parallel fibers 2–6 mm long (Mugnaini, 1983). Granule cells are targets of the afferent mossy fibers and provide the main source of intracortical excitatory drive.

The activity of granule cells is regulated by another type of excitatory interneurons, unipolar brush cells (UBC). UBCs possess a single dendrite receiving a prominent input from corticopetal mossy fibers (Mugnaini et al., 2011). UBC axons form asymmetric synapses with dendrites of granule cells. The mono- and disynaptic excitation granule cells receive from mossy fibers and UBC axons enhances the propagation and summation of excitatory drive from the primary vestibular afferents (Kalinichenko, Okhotin, 2005).

The inhibitory elements in the cerebellar cortex comprise several types of GABAergic neurons and Purkinje cells. The latter give rise to efferents to the cerebellar cortex. Basket and candelabrum cells form, respectively, axosomatic and axodendritic synapses with Purkinje cells (Lainé, Axelrad, 1994; Flace et al., 2004). Golgi cells are the largest inhibitory interneurons in the cerebellar cortex. They mono- and disynaptically inhibit basket and Purkinje cells, respectively. This inhibition may be both direct and recurrent (De Schutter et al., 2000). The direct inhibition is mediated by basket-to-Purkinje cell synapses and efferent connections of Purkinje cells with neurons of the deep cerebellar nuclei, while the recurrent inhibition occurs via granule-to-Golgi cell and Golgi-to-granule cell inputs. Lugaro cells synapse to basket cell bodies and axonal hillocks and to Golgi cell dendrites and, in turn, receive inputs from serotonergic afferent fibers and recurrent collaterals of Purkinje cell axons. Lugaro cell firing induces rhythmic activity in local neural circuits. The effects of Lugaro cells are mediated by the feedback system involved in Purkinje cell disinhibition (Dieudonné,