Neurons of the Deep Cerebellar Nuclei

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Marylka Yoe Uusisaari and Thomas Knöpfel

Abstract

The cerebellar nuclei (CN) are the final processing unit of the cerebellar circuitry, essentially combining most of cerebellar afferent inputs with the output of cerebellar cortex, transmitting the result of this integration to the extracerebellar targets, placing them at a key position in understanding cerebellar function on system level. Until recently, the nuclei have been treated as a simple relay nucleus with little neuronal diversity or computational capability. However, with the advent of genetically encoded fluorescent labels, the complexity and diversity of the CN neuronal circuits has started to become clear, rising doubts on the simplistic view of CN role in cerebellar computation.

In this chapter, the currently known CN neuronal types – in all, four projecting neuron and two interneuron types – are described, and recommendations on their electrophysiological identification (in mouse slice preparation) are provided.

M.Y. Uusisaari (✉)
Laboratory for Neuronal Circuit Dynamics, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako City, Saitama, 351-0198, Japan
and
Theoretical and Experimental Neurobiology Unit, Okinawa Institute of Science and Technology (OIST), 1919-1, Tancha, Onna–Son, Okinawa, 904-2423, Japan
e-mail: yoe@iki.fi

T. Knöpfel
Laboratory for Neuronal Circuit Dynamics, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako City, Saitama, 351-0198, Japan
e-mail: tknopfel@brain.riken.jp

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Introduction

The afferent and efferent synaptic connections of the cerebellar nuclei (CN) places them in a key position where they can integrate signals from the brain stem, the inferior olive, and the spinal cord with the output from cerebellar cortex and to provide the major efferent pathway of the cerebellum. While this conclusion can be derived based on purely anatomical knowledge, electrophysiological data are required to define the level of complexity at which the CN integrate incoming signals to generate their output. It is largely unknown to which extent the CN contributes to the generation of signals that are attributed to cerebellar function such as timing signals and temporal patterns. Arguments against a simple relay function of the CN include the indications that at least a portion of motor memory is stored in the CN (Wada et al. 2007). As a first step toward understanding operations that are accomplished by the neuronal circuits of the CN, the major circuit elements – the major CN neuronal types – are now identified and characterized. The aim of this chapter is to summarize the efforts made in several laboratories toward this goal. We mostly focus on the lateral CN and data described in a series of works (Uusisaari et al. 2007; Uusisaari and Knöpfel 2008, 2009, 2010; Bagnall et al. 2009) that are based on an approach that combines morphological examination and analysis of the intrinsic and synaptic electrophysiological properties together with genetic labeling of the various neurotransmitter types (GABAergic and glycinergic neurons). For detailed discussions on the rationales underlying the present classification of CN neurons, the reader is directed to the original publications as well as a recent review of the CN circuitry (Uusisaari et al. 2007; Uusisaari and Knöpfel 2008, 2009, 2010; Bagnall et al. 2009; Uusisaari and De Schutter 2011). Table 46.1 provides an overview and basic properties of the six types of neurons that have been characterized to date; Fig. 46.1 shows representative examples of biocytin-stained neurons of the five CN neuron types examined in the authors' laboratory.

Projection Neurons

As the CN are the main output structure of the entire cerebellum, their projection neurons have initially received the most attention among the CN cell types. Based on their putative transmitter, the projection neurons are subdivided into glutamatergic, GABAergic, and glycinergic groups. At present, physiological data are too incomplete to further subdivide these groups into functionally distinct subpopulations.

Large Glutamatergic Projection Neurons

The largest and best-characterized group of CN neurons are the large glutamatergic projection neurons ("GADnL"; Uusisaari et al. 2007). As was described by Chan-Palay in her seminal work (Chan-Palay 1977) as well as by others

Table 46.1 CN neuronal types and their basic properties

	GADnL	NO	GAD+	GADnS	Gly-I	Gly-F (Bagnall et al. 2009)
Type	Projection	Projection	Local	Local	Projection	Projection
Neurotransmitter	Glutamate	GABA	GABA/ glycine	Glutamate (?)	Glycine (?)	Glycine
Soma diameter (μm)	20–35	5–15 (?)	10–20	15–25	20–25	Area 189 ± 67.5 μm^2
AP half-width (ms)	<0.6 ms	0.7–1.2 (?)	0.7–1.2	0.5–1	0.5–1	0.5–1 (+33 °C)
AHP type	Fast + slow	Slow	Slow	Fast + slow	Fast + slow	Fast + slow
Spontaneous firing (Hz)	15–30	6–10 (?)	5–12	15	<1	?
Max. sustained firing (Hz)	>200	?	50	50	NA	>200 (+33 °C)
Frequency accommodation ratio	0.7	?	0.5	0.5	0.4	?
Purkinje neuron innervation demonstrated	Yes	Yes (anatomically)	No	Yes	No	Yes

Electrophysiological parameters were measured at room temperature unless stated otherwise. Abbreviations: GADnL, large glutamatergic projection neuron; NO, GABAergic nucleoolivary neuron; GAD+, GABAergic (possibly glycinergic) interneuron; GADnS, small non-GABAergic (putatively glutamatergic) local neuron; Gly-I, glycinergic projection neuron in the lateral CN; Gly-F, glycinergic projection neuron in the fastigial nucleus (Bagnall et al. 2009); NA, not applicable (Gly-I neurons do not fire spontaneously); question marks denote data that is not available or only preliminary.

(Sultan et al. 2002; Aizenman et al. 2003; Uusisaari et al. 2007), the morphological parameters of these cells are broadly distributed. It is still unclear if this diversity reflects specialized integrative properties or connectivity constrains (e.g., sampling of synaptic inputs, target structure). However, despite the efforts in correlating morphology with intrinsic physiological properties, no criteria have emerged that would allow for division the GADnL cells into subpopulations with distinct intrinsic properties. Therefore, they are presently pooled into a single group of neurons, even though it is possible or even likely that more detailed examinations in future will lead to a refined description of this cell type.

The glutamatergic projection neurons are the largest of CN cell types, and indeed, they are comparable in size to the Purkinje neurons (PNs) in terms of cell body diameter and maximal dendritic extension (Uusisaari et al. 2007; Aizenman et al. 2003), even though the PN dendritic trees are clearly more densely branched to accommodate their very large number of parallel fiber synapses. Indeed, the GADnL neuron dendritic trees can span the major part of an individual CN subnucleus (see Figs. 7–10 in Chan-Palay 1973). This feature suggests that these neurons are capable of sampling synaptic inputs over large areas of the cerebellar

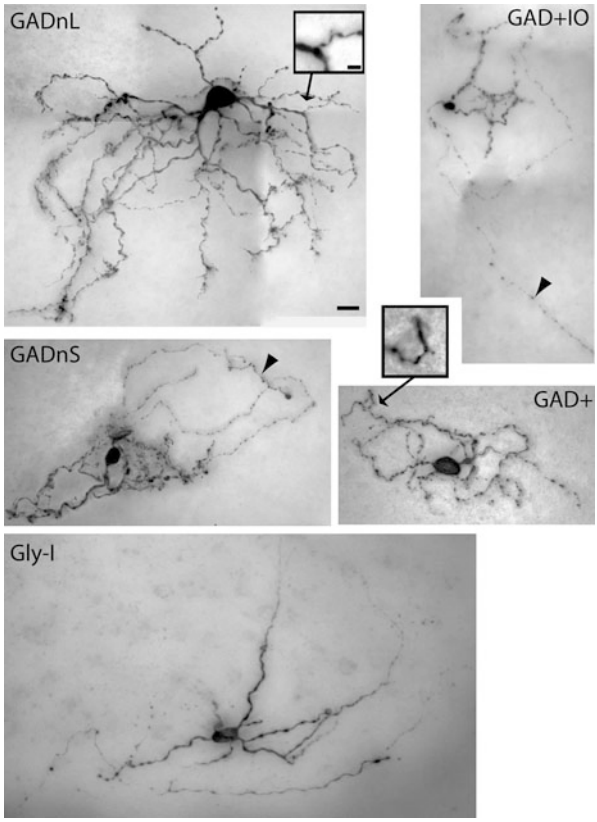

Fig. 46.1 Representative examples of biocytin-stained cells of various CN cell subtype. GADnL, large glutamatergic projection neuron. Inset shows a small dendritic branch with spines. GAD+IO, GABAergic IO-projecting neuron. *Arrowhead* points to an efferent axon. GADnS, small non-GABAergic (putatively glutamatergic) local neuron. *Arrow* points to an axon that branches near the neuron's own dendritic field. GAD+, GABAergic or GABA/glycinergic local neuron. Inset shows a dendritic branch with spines. Gly-I, glycinergic projection neuron. Scale bar in GADnL (corresponds to all figures), 20 μm; scale bar in insets, 5 μm

cortical somatotopic map. Accordingly, the GADnL neurons are the target of a large number of PN axonal terminals that virtually cover their cell bodies and large parts of the dendritic synaptic space. Experimental and theoretical studies suggest that the PNs can have a powerful control over the activity of these neurons (Gauck and Jaeger 2000; Lang and Blenkinsop 2011) and a rise in PN activity can prevent their spontaneous firing while they may undergo depolarization block in the effective absence of GABAergic control (Raman et al. 2000). Interestingly, a massive spontaneous, asynchronous GABA release (presumably from the PN terminals) can be observed in slice preparations where most of the connections between the CN and the cerebellar cortex are cut. This spontaneous GABA release, hence, likely occurs independent from PN somatic action potentials, and its presence highlights the critical importance of GABAergic control of the CN GADnL glutamatergic projection neurons. GADnL neurons, like the majority of all other CN neurons, spontaneously fire action potentials, even in the absence of synaptic input. The frequency of this intrinsic ("resting") action potential generation is highest in GADnL among all CN neurons and ranges from 20 Hz in slices to up to 60 Hz in vivo (e.g., Rowland and Jaeger 2005). During behavioral tasks, spiking

frequency can transiently increase to 160 Hz (Thach 1968). In response to long-lasting direct current injections, GADnL neurons exhibit only a weak frequency adaptation, endowing them with the capability to relay tonic, frequency-coded signals.

Small, GABAergic Projection Neurons

Contrary to the extensive electrophysiological examination of the glutamatergic projection neurons, the second major cerebellar efferent pathway – the purely GABAergic (de Zeeuw et al. 1994) connection from the CN to the inferior olive – remains poorly explored in terms of intrinsic and synaptic electrophysiology. It is well known that the nucleoolivary (NO) projection is strictly separate from the nucleorubral and nucleothalamic projections in terms of efferent neuronal populations (Teune et al. 1995). The GABAergic cells that give rise to this projection are small-bodied (long axis up to 10–15 μm) and concentrate in the ventrolateral area of the dentate nuclei. A rigorous electrophysiological study of these cells is still pending, but the few available recordings (see Uusisaari and Knöpfel 2010) suggest that they, like most of other CN cell types, are spontaneously active, generating action potentials at frequencies up to 10 Hz.

It has been shown (Teune et al. 1998; De Zeeuw et al. 1997) that the nucleoolivary projection neurons are targeted by Purkinje neuron axons, and indirect evidence suggests that the PNs have, via this connection, a functionally significant influence on IO rythmogenesis and complex spike activity in the cerebellar cortex (Chen et al. 2010; Andersson et al. 1988). The physiological significance of these connections seems evident, but possible inputs from within the CN to NO neurons have not been elucidated.

Glycinergic Projection Neurons: Nucleocortical and Nucleovestibular

The recent availability of transgenic mice in which glycinergic neurons express a fluorescent protein (driven by the promoter for GlyT2; Zeilhofer et al. 2005) has allowed a targeted electrophysiological and morphological examination of the glycinergic neuron population in the CN (Uusisaari and Knöpfel 2009; Bagnall et al. 2009). These studies confirmed earlier immunohistochemical reports that all CN harbor glycinergic neurons, most of which have been thought to represent mixed GABAergic/glycinergic local neurons (Chen and Hillman 1993). Examination of the GlyT2-positive neurons in slices (Uusisaari and Knöpfel 2009; Bagnall et al. 2009) revealed that, in addition, the lateral and fastigial nuclei each have a specific population of glycinergic projection neurons that project to the cerebellar cortex (Uusisaari and Knöpfel 2009) and the vestibular nuclei (Bagnall et al. 2009), respectively. These only recently described pathways provide for inhibitory efferent communication from the CN to these areas.

The nucleocortical glycinergic neurons are unique among the CN neurons in that unlike all other cells thus far described, they do not generate action potentials in the absence of depolarizing (synaptic) drive; furthermore, they are not able to maintain constant firing rates even in response to direct current injection. When depolarized, these cells respond with a burst of short action potentials at high frequency (up to 130 Hz). Following this burst, they remain in depolarization block due to inactivation of spike-generating currents until repolarized.

The cellular targets of the Gly-I neurons within the cerebellar cortex have not yet been rigorously established. It is known, however, that in most parts of the cerebellar cortex, glycinergic receptors are only found on cerebellar Golgi cells, identifying them as the putative target of Gly-I neurons. Assuming that this is the case, activation of Gly-I neurons would result in a transient inhibition of Golgi cells and consequently disinhibition of granule cells. This mechanism could provide a time window during which transmission of mossy fiber signals to the cerebellar cortex are facilitated (Kistler et al. 2000; D'Angelo and De Zeeuw 2009). Further examination of these neurons is required for elucidation of their effect on their cortical targets as well as the synaptic inputs impinging on them. Moreover, since unipolar brush cells in the vestibulocerebellum are also known to express glycine receptors, they are another putative target of nucleocortical inhibitory control.

In contrast to the Gly-I cells, the glycinergic projection neurons in the rostral fastigial nuclei are capable of maintaining high firing rates (Bagnall et al. 2009). Also, they have been more robustly characterized in terms of their projection targets (Bagnall et al. 2009), showing that they mediate direct, tonic inhibitory influence on vestibular nuclear neurons.

Interneurons

Despite the strong interest in the properties of CN projection neurons as the determinants of cerebellar output, it should be remembered that the dynamical behavior of a neuronal network is largely determined by the properties and connections of interneurons. Even though the precise wiring pattern of intrinsic connections within the CN is still largely unknown, there is strong evidence for the existence of a variety of local synaptic connections among the projection neurons as well as purely local neuronal populations. As is the case in other brain areas, it is likely that the classification of these cells will be refined as future studies will reveal a larger variety of interneuronal elements.

GABAergic/Glycinergic Interneurons

The projection neurons of the CN are intermingled with GABAergic neurons with axons terminating within the CN. At least a fraction of these GAD+ cells (they contain the GABA-synthesizing enzyme glutamic acid decarboxylase; GAD) are also GlyT2+, strongly suggesting that they use glycine as a cotransmitter.

These cells are characterized by smaller cell bodies (10–20 μm) than the glutamatergic projection neurons. Their spherical or fusiform cell bodies give rise to less elaborate dendritic trees that cover a smaller area, extending on average not further than 150 μm. Even though detailed reconstruction of interneuronal axonal target fields are still missing, they seem to be most likely targeting synapses on distal rather than proximal dendrites of various other CN cell types.

In contrast to the general "rule" of other brain areas that GABAergic interneurons characteristically fire short, nonaccommodating action potentials at high frequencies, the GABAergic interneurons in CN have different properties. Indeed, compared to the CN projection neurons, their action potentials are broad and the mean firing rates saturate near 50 Hz. These two features might be related to a possible lower expression levels of Kv3 subtypes (McMahon et al. 2004; Alonso-Espinaco et al. 2008) that result in weaker and slower after hyperpolarization, that in turn affects the cell's ability to maintain high firing rates (Akemann and Knöpfel 2006). GABAergic interneurons also show more pronounced frequency adaptation compared to the glutamatergic projection neurons, that makes them better-suited for extracting and transmitting phasic signals (e.g., changes in input signal frequency) rather than tonic signals (e.g., rate coding of input signal frequency) like the glutamatergic projection neurons. In line with this view, the GABAergic interneurons show also somewhat stronger tendencies toward postinhibitory rebound activity as compared to the tonic-firing glutamatergic projection neurons.

Finally, in disagreement with the often-held assumption that the Purkinje neurons target all CN neurons equally, it seems that the GABAergic interneurons differ significantly in this respect from the glutamatergic CN neurons (both projecting and local ones, see below): instead of being continuously bombarded by large spontaneous GABAergic synaptic events in slice preparations, the GABAergic interneurons seem to receive only sparse (up to 2 Hz) and small (up to 100 pA) synaptic currents that also show much slower kinetics (decay time constant up to 20 ms in room temperature). Furthermore, unlike the glutamatergic neurons where large majority of the GABAergic synapses is localized on somatic and proximal dendritic membranes, it seems that the GABAergic synapses in GABAergic interneurons reside on more distal dendrites. It would thus seem that whereas in glutamatergic neurons the GABAergic synapses would be perfectly arranged to precisely control AP generation, in the GABAergic interneurons, the role of GABAergic inhibition would rather be related to modulation of dendritic integration. In fact, it may be that these interneurons are only sparsely or even not at all targeted by the Purkinje neurons. If this possibility holds true, these cells would be positioned to control CN output rather independent of the cerebellar cortex.

Non-GABAergic (Putatively Glutamatergic) Interneurons

Even though the term "interneuron" is sometimes incorrectly thought of as a synonym for "GABAergic neuron," glutamatergic interneurons (neurons that

synapse only with neighboring cells) are known to exist in various brain areas, such as Pre-Bötzinger complex (Stornetta et al. 2003), septohippocampal pathway (Wu et al. 2003), and also as unipolar brush cells in the cerebellar granular layer (Diño et al. 2000). Similarly, the CN contain neurons whose axonal terminations are strictly confined to the nucleus but do not express GAD67 and therefore are likely glutamatergic interneurons ("GADnS"; Uusisaari et al. 2007). These cells are as abundant as the GABAergic interneurons. While similar to GAD+ cells with respect to their morphological features, these non-GABAergic interneurons differ significantly from their GABAergic counterparts as well as the glutamatergic projection neurons in their electrophysiological properties.

Firstly, even though the maximal firing rates of GADnS neurons are lower than in the GADnL neurons, they fire significantly shorter action potentials with less frequency adaptation than the GAD+ neurons. This potentially makes them suited better for linear encoding of synaptic input than the GAD+ neurons. Secondly, the GADnS are closer to the GADnL neurons in terms of the frequency, kinetics, and apparent subcellular origin of the GABAergic synaptic inputs, suggesting that they are under similar Purkinje neuron-originating inhibitory influence as the GADnL neurons. It should be noted that the cell-type-specific Purkinje neuron projection patterns (in terms of density, divergence, and convergence) are currently unknown.

Summary

Presently, six CN neuronal types have been described with distinct electrophysiological morphological and biochemical properties. The diversity of cell types and the complexity of CN circuitries are still somewhat underappreciated, but available information already provides indications that the CN are endowed with the ability to perform complex computations that extend beyond their traditionally attributed "simple relay" function.

The present classification was developed using genetically modified mice in which cellular populations are highlighted by fluorescent proteins. Caution is, however, recommended in predicting the transmitter function from the presence of genetic markers for enzymes and receptors. Thus, in the absence of a direct marker for glutamatergic neurotransmitter type, neurons that express neither GAD67 nor GlyT2 are only putatively glutamatergic. Ultimately, the neurotransmitter type used by these cells needs to be shown using paired recordings and confirming the pharmacological profile of the synaptic responses.

In the absence of fluorescent labels, the following approach for experimentalists wishing to identify their target neurons in lateral CN slices is recommended: First, the spontaneous firing frequency (with no bias current) and AP shape should be assessed; neurons with frequencies lower than 10 Hz, AP half-widths of more than 1 ms (at physiological temperatures), and with no clear fast AHP are most likely the GABAergic neurons. The distinction between GABAergic interneurons and IO-projecting nucleoolivary (NO) neurons is not thoroughly described, but the IO

neurons are smaller than the GABAergic interneurons (e.g., have a smaller electrical capacitance) and also they are preferably clustered around the ventrolateral border of the nuclei (Giaquinta et al. 1999).

Neurons with faster (up to 15 Hz), sustained firing frequencies with no bias current and shorter action potentials correspond to the non-GABAergic (presumedly glutamatergic) neurons, with the local neurons exhibiting lower maximal firing rates (not more than 50 Hz); they are also identifiable by their smaller size (in our hands, an approximate boundary of 100 pF (mouse) has proven a useful criterion between "large" and "small" in this respect). Another useful feature is the presence of large-amplitude, high-frequency spontaneous GABAergic synaptic conductances in the glutamatergic CN neurons.

Finally, the glycinergic projection neurons in the lateral nucleus can be identified by their relatively large size (around 20–25 μm), hyperpolarized resting membrane potentials, and extremely strong frequency adaptation that in essence prevents them from maintaining steady firing rates much above 50 Hz.

Further examinations of the diversity of intrinsic properties as well as connectivity patterns are needed for more complete understanding of the computational capabilities of this structure. However, the knowledge on the diversity of CN cell subgroups is already enough advanced to be taken into consideration when designing further experiments in this structure.

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