Chapter 42
Cerebellar Nuclei

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Abstract Understanding the basic physiology of cerebellar nuclei (CN) is essential to the understanding of cerebellar function and disorders as they provide the only output from the cerebellum along with the vestibular nuclei. In addition to integrating the inhibitory input from cerebellar cortical Purkinje cells, CN neurons also receive direct excitation from mossy fibers and this direct excitatory input to the CN may in fact drive a number of behaviorally relevant activities. The complete picture is considerably more complex than that of a simple relay of incoming excitation and inhibition, however. Specifically, the functional significance of synaptic plasticity in the CN, high spontaneous spike rates, post-inhibitory rebound firing, and multiple output pathways including GABAergic inhibition feeding back to the inferior olive remain to be elucidated.

Keywords Deep cerebellar nuclei • Inhibition • Excitation • Rebound spiking • Long-term plasticity • Short-term plasticity • Ion channel • GABA • Synchrony • Complex spike • Collateral • Climbing fiber • Mossy fiber • Pacemaker • Eye movement • Vestibular • Timing

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42.1 Basic Physiology of CN Neurons

42.1.1 Cellular Physiology

CN neurons recorded in brain slices from any of the 4 nuclei present in rodents (lateral, anterior interposed, posterior interposed, and medial) are spontaneously regularly spiking (Jahnsen 1986), a property which is due to an intrinsic depolarizing plateau current (Raman et al. 2000). A robust property of CN neurons is their ability to fire rebound spike bursts following strong hyperpolarization induced by current injection (Llinas and Muhlethaler 1988; Jahnsen 1986; Aizenman and Linden 1999). The rebound activity has an initial fast burst component carried by T-type calcium currents (Molineux et al. 2006) and a longer-lasting 2–5 s increase of spike rate associated with persistent sodium currents (Sangrey and Jaeger 2010). The functional implications of CN rebound properties are still hotly debated (Alvĩa et al. 2008; Hoebeek et al. 2010). While these basic properties are present in excitatory and inhibitory CN neurons, GABAergic cells can be distinguished physiologically by a broader spike width, a slower spike-afterhyperpolarization, and higher spike rate accommodation, and further differences are present between morphologically larger and smaller non-GABAergic neurons (Uusisaari et al. 2007).

42.1.2 Synaptic Physiology and Synaptic Plasticity

Early in vitro studies provided direct evidence that Purkinje cell spiking causes monosynaptic inhibitory post-synaptic potentials (IPSPs) in the CN (Ito et al. 1964). These IPSPs are characterized by a large amplitude, a fast decay, and pronounced short term depression (Person and Raman 2012). A single CN neuron receives large IPSPs from about 40 Purkinje cells, while smaller IPSPs may derive from many more Purkinje cells with fewer and/or more distal synaptic terminals (Person and Raman 2012). Robust excitatory postsynaptic potentials (EPSPs) can be elicited by stimulation of mossy fibers (Llinas and Muhlethaler 1988), which are collaterals of the same fibers projecting to cerebellar cortex (Shinoda et al. 1992). Climbing fibers also collateralize in the CN (Sugihara et al. 1999), and may induce a spike response in vivo (Blenkinsop and Lang 2011).

Long-term plasticity has also been observed for synaptic inputs to the CN. Excitatory mossy fibers undergo long-term potentiation as a result of a distinct combination of inhibitory and excitatory inputs “that resemble the activity of Purkinje and mossy fiber afferents that is predicted to occur during cerebellar associative learning tasks” (Pugh and Raman 2009). Inhibitory Purkinje cell input can undergo either long-term potentiation or long-term depression, which is dependent on the amount of rebound depolarization produced by a burst of Purkinje cell inputs (Aizenman et al. 1998). The plasticity inducing protocols in the CN generally require complex temporal conditions of excitation and inhibition, which may relate to the commonly hypothesized role of the cerebellum in motor timing.

42.2 A View at CN Function

42.2.1 Behavioral Correlates of CN Activity Changes

A substantial number of studies has been undertaken to study the spiking activity of CN neurons in behaving animals, often revealing complex relationships between CN spike rate increases or decreases and sensory stimuli as well as movements. One of the most studied behaviors with respect to CN activity is the delayed eye blink reflex, where CN activity is clearly related to the learnt timing of the motor command (Thompson and Steinmetz 2009). In a more general sense CN output activity is congruent with representing an internal or forward model of movement execution (Lisberger 2009; Miall and Reckess 2002) that is important in the predictive control of behavior.

42.2.2 Multiple Functional Areas in the CN and Microzonal Organziation

Each CN nucleus and to some degree different areas in each nucleus will be engaged in controlling behaviors related to the anatomical inputs of the respective nucleus, such as the vestibulo-ocular reflex and control of balance in the vestibular nuclei (Lisberger and Miles 1980), limb movements in the interposed and dentate nuclei (Strick 1983), and cognitive aspects of timing tasks such as finger tapping also in the dentate nucleus (Stefanescu et al. 2013). The microzonal organization of the cerebellar cortex is preserved in the CN (Apps and Garwicz 2000). This allows for functionally relevant climbing fiber synchrony evoking complex spikes in cerebellar cortical microzones to converge in the CN and elicit behaviorally relevant responses that may depend on this synchrony (De Gruijl et al. 2014; Person and Raman 2012).

42.2.3 Output of the CN Is Split into Distinctive Pathways

GABAergic neurons in CN solely project to the inferior olive where they often terminate near gap junctions in olivary glomeruli (De Zeeuw et al. 1998). This arrangement allows CN output to influence both the occurrence and the synchrony of olivary spikes (Lefler et al. 2014), which may be important in controlling olivary motor error signals (Simpson et al. 1996).

Excitatory CN neurons project to a variety of targets, notably the motor thalamus, red nucleus, and brainstem motor nuclei. The functional impact of CN activity on these targets is often not clearly understood, but given the high tonic rates of CN firing in vivo and behaviorally related phasic and tonic changes in CN firing a temporally highly precise effect on motor performance is expected (Heck et al. 2013).

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