# Chapter 41
# Rebound Depolarization and Potentiation

**Steven Dykstra and Ray W. Turner**

**Abstract** The deep cerebellar nuclei (DCN) are critical in defining the output of cerebellum. The DCN are positioned at the base of cerebellum where they receive collateral input from afferent excitatory mossy and climbing fiber inputs and GABAergic inhibitory input from Purkinje cells of cerebellar cortex. DCN cells exhibit a form of rebound membrane depolarization following a hyperpolarization that gives rise to a rebound spike burst. Intracellular recordings and calcium imaging have established roles for virtually all classes of calcium channels in the rebound response, with additional roles for sodium, HCN, and potassium channels. Long-term potentiation of mossy fiber inputs is further known to rely on ion channels involved in the rebound response, revealing a complex interplay that determines DCN cell excitability and thus the final output from cerebellum.

**Keywords** Deep cerebellar nuclei • Rebound burst • Long-term potentiation • Calcium channel

## 41.1 Encoding Purkinje Cell Input

The final output of all signal processing in cerebellar cortex (not including vestibular input) is communicated by neurons in the DCN, identified as medial, interposed and lateral nuclei in rodents. DCN cells receive collateral excitatory projections from mossy and climbing fibers ascending to cerebellar cortex and extensive GABAergic inhibition from cerebellar cortical Purkinje cells. To encode Purkinje cell inhibitory input DCN cells exhibit a rather unique capability of generating a rebound increase in firing following a membrane hyperpolarization. Recent work has further identified how long-term potentiation (LTP) of synaptic inputs depends on an interplay with the ion channels that underlie a rebound response.

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### *41.1.1 Rebound Responses*

Membrane hyperpolarizations invoke rebound responses in DCN cells that are reflected in an early peak increase in firing frequency (within 100 ms) and a second late phase of rebound firing that can last for seconds. The role(s) for rebound responses in DCN cells is not entirely understood. Rebound firing has been implicated in rate and phase coding of Purkinje cell input, as well as modifying the timing, reliability, and precision of spike firing following a hyperpolarization (Hoebeek et al. 2010; Pedroarena 2010; Engbers et al. 2011; Person and Raman 2012; Steuber and Jaeger 2012). Most work in vitro on rebound discharge has focused on presumed excitatory "large diameter" cells (>15 μm), although the activity of more cell types is being distinguished through labeling of GABAergic and glycinergic cell types (Uusisaari et al. 2007, Uusisaari and Knopfel 2012). Different rebound phenotypes are still being defined, with several different patterns reported following hyperpolarizing stimuli (Fig. 41.1a, b) (Czubayko et al. 2001; Hoebeek et al. 2010; Pedroarena 2010; Tadayonnejad et al. 2010; Engbers et al. 2011).

### *41.1.2 Ionic Basis for Rebound Responses*

Several ion channels are known to contribute to rebound responses. T-type calcium channels are partially inactivated during the resting tonic discharge of DCN cells, with hyperpolarizations acting to remove inactivation. A return to resting potential then triggers a larger T-type current (calcium spike) to drive a rebound depolarization (Molineux et al. 2006, 2008; Alvina et al. 2009; Tadayonnejad et al. 2010; Engbers et al. 2011; Steuber and Jaeger 2012; Schneider et al. 2013). The hyperpolarization-activated cyclic nucleotide-gated (HCN) channel is directly activated by membrane hyperpolarization in DCN cells, and upon return to resting potential deactivates slowly enough to generate a depolarization that controls first spike latency and spike precision, and augments the role of T-type current by shortening the membrane time constant (Raman et al. 2000; Sangrey and Jaeger 2010; Engbers et al. 2011). Non-inactivating sodium current(s) are proposed to contribute to at least the slow phase of rebound, as these channels will also undergo inactivation at rest and recovery from inactivation during a hyperpolarization. Return to resting potential then evokes a slowly inactivating sodium current that helps drive the late rebound component (plateau depolarization) (Jahnsen 1986; Llinas and Muhlethaler 1988; Aman and Raman 2007; Sangrey and Jaeger 2010). Recent work suggests a contribution by virtually all classes of high voltage-activated calcium channels, as defined by selective pharmacological blockers (Zheng and Raman 2009). The role of potassium channels has been considered, with pharmacological, knockout animal, and dynamic clamp studies uncovering differences in the role of

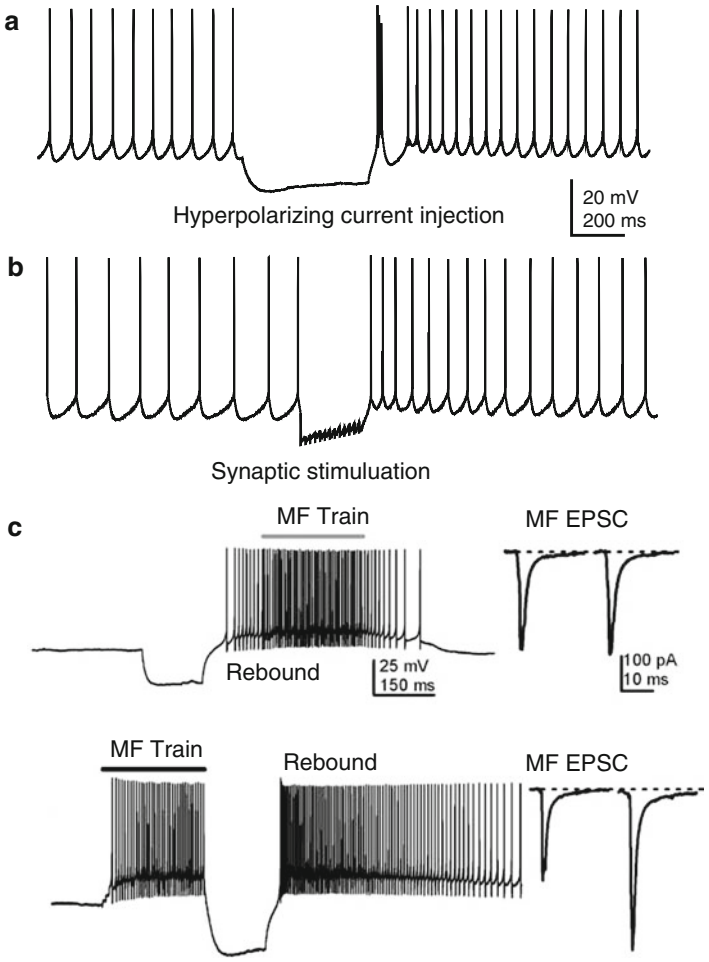


**Fig. 41.1** (**a**, **b**) Representative recordings of spike output from two large diameter DCN cells exhibiting spontaneous discharge. (**a**) Injecting a 500 ms current step elicits a transient rebound response. (**b**) A 25 pulse 50 Hz train of synaptic inhibitory inputs elicits a weak rebound response. (**c**) Induction of LTP of mossy fiber (MF) inputs. At *left* are responses evoked by different induction protocols and on *right* EPSCs before and after the induction protocols. Protocols consisted of a 250 ms, 133 Hz stimulation of excitatory afferents and a 150 ms current injection to ~ −85 mV. LTP of EPSCs occurs in relation to synaptic input trains that precede a rebound spike response. Data in (**c**) was modified from Pugh and Raman (2008) (Republished with permission of the Society for Neuroscience, from Mechanisms of Potentiation of Mossy Fiber EPSCs in the Cerebellar Nuclei by Coincident Synaptic Excitation and Inhibition, Pugh and Raman (2008); permission conveyed through Copyright Clearance Center, Inc)

voltage- or calcium-gated potassium channels in controlling tonic firing vs rebound responses (Aizenman and Linden 1999; Alvina and Khodakhah 2008; Molineux et al. 2008; Joho and Hurlock 2009; Pedroarena 2011; Feng et al. 2013).

## 41.2 LTP of Mossy Fiber Input and Rebound Responses

The ion channels that are activated during the rebound response also help shape synaptic plasticity in the DCN. One example is the induction of mossy fiber LTP onto DCN cells that requires co-activation of excitatory and inhibitory synaptic inputs, but not according to classical Hebbian rules of coincidence. Rather, LTP at this synapse is induced if a train of mossy fiber input precedes a hyperpolarization and rebound response (Fig. 41.1c) (Pugh and Raman 2008; Person and Raman 2010; Zheng and Raman 2010). Potentiation thus follows a priming rule of synaptic plasticity, where potentiation is dependent on the timing of stimuli that trigger specific calcium-dependent signalling cascades that act as either a local priming signal or as a global potentiating signal. Specifically, mossy fibers prime a subset of synaptic inputs through a pathway that is dependent on activation of NMDA receptors and the phosphatase calcineurin. If the DCN cell is then hyperpolarized due to Purkinje cell input, calcium influx through L-type calcium channels normally present during tonic resting discharge is reduced, with a subsequent rebound response activating α-CaMKII as the global triggering signal for LTP (Pugh and Raman 2008; Person and Raman 2010; Zheng and Raman 2010). A unique aspect of this form of LTP is the extent to which it fits models of cerebellar learning and memory formation in a system that is tonically active under resting conditions (Zheng and Raman 2010), and highlights how a rebound response can be utilized in novel ways to control the output of cerebellum at the level of the DCN.

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