Chapter 40
Simple Spikes and Complex Spikes

Thomas S. Otis

Abstract Cerebellar Purkinje neurons communicate with downstream circuit elements by generating two distinct types of electrical activity. Purkinje neurons fire conventional action potentials, termed *simple spikes*, and they also intermittently fire a highly stereotyped burst of decrementing spikes, called a *complex spike*. Each of these types of electrical activity arises from an interaction between synaptic input and distinct excitability mechanisms intrinsic to Purkinje neurons. Simple spikes occur at very high frequencies in the range of 50 spikes per second and are driven by pacemaking ion channels expressed by Purkinje neurons. This high simple spike rate is then modulated by excitatory and inhibitory synaptic input. Complex spikes occur in response to excitatory synaptic input from the climbing fiber; these compound electrical events are driven in part by the large voltage-gated calcium conductance in the dendrites of Purkinje neurons. Finally, the two forms of excitability interact; complex spikes can exert indirect effects on simple spike firing rate. Together, these two firing behaviors endow Purkinje neurons with a range of signaling behaviors critical for cerebellar contributions to motor coordination and motor learning.

Keywords Motor learning • Purkinje neuron • Excitability • Ion channel • Resurgent current • Climbing fiber

40.1 Simple and Complex Spikes

Purkinje neurons (PNs) are unusual neurons and this is particularly true of their highly distinctive electrical excitability. PNs generate two types of regenerative electrical behavior. As do most other neurons, they fire typical, voltage-gated sodium channel-dependent action potentials which are termed simple spikes. In addition, they also generate distinctive burst responses that are characterized by sodium channel driven "spikelets" riding on a depolarized plateau potential (see

T.S. Otis (✉)
Department of Neurobiology and Integrated Center for Learning and Memory, Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA
e-mail: otist@ucla.edu

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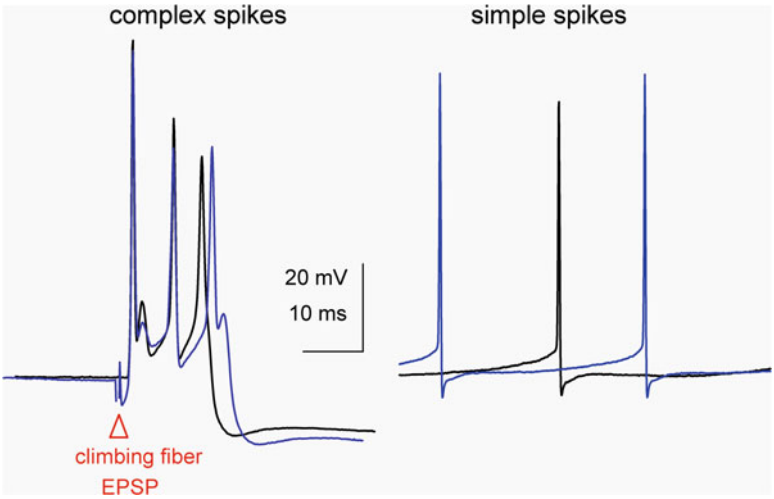

Fig. 40.1 Examples of complex spikes in response to electrical stimulation of the climbing fiber input (*red triangle*) and spontaneously occurring simple spikes. Each panel shows two superimposed trials, one *blue* and one *black*

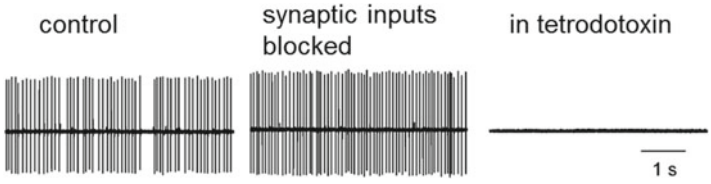

Fig. 40.2 Extracellular recording of PN pacemaking under the indicated conditions

Fig. 40.1). Such bursts, which are known as complex spikes, occur in response to the very large excitatory synaptic input provided by the single climbing fiber axon that innervates each PN. Below we discuss fundamental physiological features of these two types of signals and their importance for information processing within the cerebellum.

40.1.1 Simple Spikes Occur at High Rates and Are Driven in Part by Intrinsic Pacemaking

Unlike conventional neurons, PNs fire action potentials constantly, even in the absence of synaptic inputs. These simple spikes occur at high rates, ranging from 40 to 100 spikes per second in resting animals. Moreover, with synaptic inputs blocked, simple spikes occur at these same high rates and with remarkable regularity (Hausser and Clark 1997)- see also Fig. 40.2. This metronome-like ability of PNs to

pacemake is a key aspect of the physiology of the cerebellum as it allows PNs to tonically inhibit their target neurons in the deep cerebellar nuclei and vestibular nuclei. Populations of PNs thus cooperate to influence motor behavior by increasing or decreasing this baseline blanket of tonic inhibition.

The ion channels responsible for this intrinsic pacemaking activity are known in some detail. The most important is a subtype of voltage-gated sodium channel called the "resurgent" sodium channel, assembled from pore-forming NaV1.6 and accessory β4 subunits (Grieco et al. 2005). Resurgent sodium channels are so named because they pass inward current as they recover from inactivation at hyperpolarized potentials between spikes, thereby generating a pacemaking drive current. In mice, missense mutations in or loss of the NaV1.6 gene result in reduced resurgent sodium current, impaired PN pacemaking activity, and ataxia (Raman et al. 1997).

Other ionic currents are also critical for pacemaking because they ensure that simple spikes are extremely brief, an important factor allowing rapid, cyclic activation of resurgent sodium channels. Spike brevity is ensured by large potassium conductances with rapid gating kinetics generated by Kv3.3, Kv3.4, and calcium activated BK channel subtypes (Raman and Bean 1999; Martina et al. 2007).

Interestingly, slowed pacemaking in Purkinje neurons is a common physiological deficit observed in transgenic mouse models of spinocerebellar ataxia (Hourez et al. 2011; Shakkottai et al. 2011; Hansen et al. 2013). These results strongly suggest that simple spike pacemaking is necessary for normal motor behavior.

40.1.2 Complex Spikes Occur in Response to Climbing Fiber Input

Mature PNs receive input from the terminal arbor of a single olivary neuron, the climbing fiber, which forms a powerful excitatory synapse onto the proximal dendritic tree. The postsynaptic response in the PN to climbing fiber input is a complex spike (Eccles et al. 1964). This burst response activates CaV3 type (a.k.a. T type) and CaV2.1 (a.k.a. P/Q type) voltage-gated calcium channels which are densely distributed throughout PN dendrites (Swensen and Bean 2003). Although dependent on membrane potential, the complex spike waveform is remarkably stereotyped (Davie et al. 2008). In this way, a single climbing fiber input can serve as a salient, cell-wide signal leading to increased calcium concentrations throughout much of the PN dendritic tree and cell soma (Tank et al. 1988; Kitamura and Hausser 2011). This is an important capability as climbing fibers convey a teaching signal to the cerebellum that drives circuit changes underlying associative forms of motor learning (Mauk et al. 1986; Raymond et al. 1996; Medina and Lisberger 2008).

40.1.3 Complex Spikes Transiently Inhibit Simple Spike Firing

Complex spikes are known to slow simple spike firing on two time scales. On a rapid time scale, complex spike transiently inhibit simple spike firing. This either results in fewer simple spikes immediately following a complex spike, termed a "post-CS pause", or it results in a period reset in which simple spike firing is phase shifted (Bell and Grimm 1969). Such rapid inhibition is due to a combination of climbing fiber-driven feedforward inhibition, and activation of SK calcium-activated potassium channels in PNs (Mathews et al. 2012). Post-CS pauses may play a role in transmitting the teaching signal to the deep cerebellar nucleus, thereby enabling circuit-wide modifications known to occur during learning (Otis et al. 2012).

On a slower time scale, complex spike rates, which typically average 1 Hz but can be suppressed or driven experimentally, show an inverse relationship with simple spike rates (Cerminara and Rawson 2004). Indeed, rates of complex spikes and simple spikes are often strongly anticorrelated in response to periodic sensory stimuli (Barmack and Yakhnitsa 2011). This anticorrelation likely arises from the same mechanisms mentioned above; however, it may also reflect learning. Repeated occurrence of complex spikes with specific patterns of parallel fiber synaptic input would result in long term changes in excitability of PNs in response to those parallel fiber inputs. In this way, the intrinsic mechanisms linking complex and simple spikes can be solidified and reinforced through experience.

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