# Chapter 21
# The Purkinje Cell: As an Integrative Machine

**Anais Grangeray, Kevin Dorgans, Sebastien Roux, and Jean-Louis Bossu**

**Abstract** The aim of this chapter is to discuss how the spontaneous activity, the simple spike and the complex spike are generated and modulated depending on the channel types expressed on the somatic and dendritic Purkinje cell membranes. Finally, we will briefly address the role of Purkinje cells in the pathology of autism.

**Keywords** Cerebellum • Purkinje cell • Spontaneous activity • Simple spike • Complex spike • Ionic channels • Autism

## 21.1 Introduction

Purkinje cells (PCs) were discovered in 1837 by a Czech anatomist, Jan Evangelista Purkyně and further nicely illustrated by Ramón y Cajal in 1899 using Golgi's staining method. PCs have a large dendritic arbor decorated with little spines. The dendritic arbor stems from a primary dendrite that emerges from a pear-shaped cell body with a single axon originating from the other end (Fig. 21.1a). PC somas align in the cerebellar cortex to form the PC layer.

PCs which are spontaneously active, receive two excitatory inputs: from the parallel fibers (PFs) and climbing fibers (CFs) (Fig. 21.1a). Those inputs provide electrical signals that are integrated and modulated along the PC dendritic tree and soma due to the presence of ionic channels. Each PC receives converging inputs from about 200,000 PF synapses. Stimulation of PF releases glutamate and produces simple spikes (SS) in PCs (Fig. 21.1b, left panel) at various frequencies. In adult animals, each PC receives one single CF originating from the inferior olive nucleus. Stimulation of CF releases glutamate on PC giving rise to a complex spike (CS): a massive electrical firing event (Fig. 21.1b, right panel). Action potentials (APs) propagate along the PC axon and trigger GABA release on their target: deep cerebellar nuclei (DCN) neurons.

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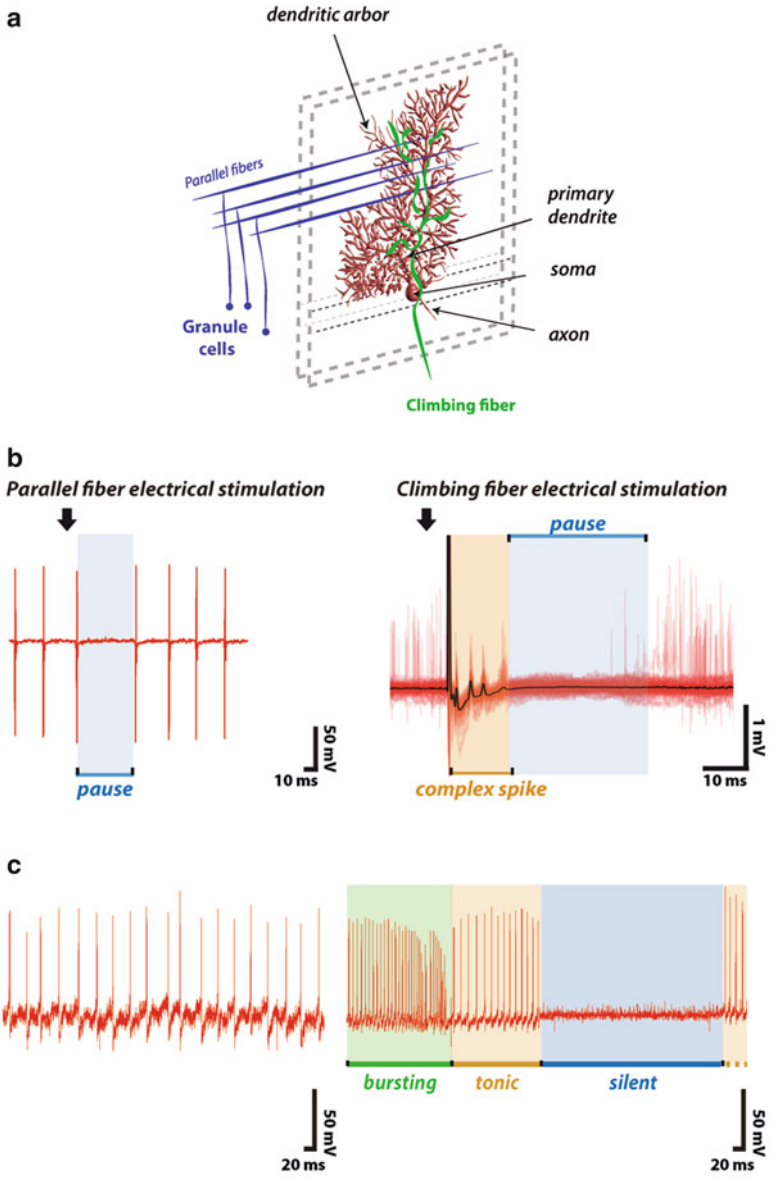


**Fig. 21.1** (**a**) 3D reconstruction of PC, afferences are also drawn. (**b**) Evoked responses of PC induced by parallel-fiber (*left*) and climbing-fiber stimulation (*right*). (**c**) Spontaneous activity of PC: an irregular discharge of AP (*left*) and a trimodal pattern of discharge (*right*)

## 21.2 Spontaneous Activity of PCs

In vivo the spontaneous activity of PCs consists in tonic SS trains at frequencies ranging between 50 and 125 Hz and CS at 1 Hz (Latham and Paul 1971). SS as well as CS are synchronized for pairs of PCs localized in the same cortical zone, this synchronization is under the control of sensory inputs (Wise et al. 2010).

This activity has a pacemaker component characterized in vitro as an irregular pattern of discharge with a frequency of 40 Hz (Fig. 21.1c, left panel). A trimodal pattern of pacemaker activity (tonic, bursting and silent modes, Fig. 21.1c, right panel) is also depicted and is probably induced by the lack of CF input.

### *21.2.1 Ionic Mechanism of the Pacemaker Activity of PCs*

PC pacemaker activity was driven by low threshold TTX sensitive $Na^+$-current and TEA sensitive $K^+$-current (Nam and Hockberger 1997; Raman and Bean 1999). Furthermore, hyperpolarization-activated current (Ih) maintains the membrane potential within a range where the inward $Na^+$-current responsible for the generation of AP firing can be activated. Thus, inhibition of the Ih current leads to quiescent periods (Williams et al. 2002). Apamin sensitive small conductance $Ca^{2+}$-activated $K^+$ channels (SK) activated by $Ca^{2+}$ entering through P-type $Ca^{2+}$ channels control the pacemaker firing frequency (Edgerton and Reinhart 2003). In PCs with a trimodal pattern, blockade of large conductance $Ca^{2+}$-activated $K^+$ channels (BK) shortened the duration of the trimodal pattern whereas dendritic $Ca^{2+}$-T-type, BK and SK channels contribute to interspike and interburst intervals. P/Q $Ca^{2+}$ channels are required to sustain spontaneous bursting. A partial blockade of P/Q channels eliminates dendritic $Ca^{2+}$-spikes and causes a switch from regular bursting to tonic firing or irregular bursting (Womack et al. 2009).

### *21.2.2 Modulation of the Spontaneous Activity of PCs*

CFs and PFs activation can modulate the PC spontaneous activity. In vivo stimulation of CFs is immediately followed by a pause in the spontaneous discharge. This effect is also depicted in PCs recorded in acute slices (Fig. 21.1b, right panel). After the pause an increase in SS activity is regularly observed and is often followed by a reduction of the SS frequency (De Zeeuw et al. 2011). In vivo removal of CF input induces an increase of spontaneous discharge frequency or even a slow oscillatory pattern of discharge. Repetitive CFs discharge can also convert the spontaneous trimodal PC discharge pattern (recorded in vitro) to a non-bursting pattern (Engbers et al. 2013).

Concerning the PFs modulation of the PC discharge, in vivo when excitatory inputs from granule cells are chronically reduced the SS firing regularity increased without alteration of the spiking frequency. Furthermore, in vitro, when the PFs are stimulated an inhibition of the spontaneous activity is depicted (Fig. 21.1b, left panel; De Zeeuw et al. 2011).

### *21.2.3 Physiological Role of the Spontaneous Activity of PCs*

The PC activity plays a role in sensory-motor calibration (Medina 2011). Interestingly, using optogenetic inhibition of PCs activity in awake mice, Heiney et al. (2014) show that a transient suppression of the spontaneous activity in a subpopulation of PCs causes discrete movements with variations in size, speed and timing depending on the duration and intensity of the inhibition.

## 21.3 The Simple Spike and the Complex Spike

### *21.3.1 The Simple Spike Induced by PFs Stimulation*

A simple electrical stimulation of PFs releases glutamate and produces small depolarizing synaptic potentials (DSPs) at many synaptic sites dispersed on the PC dendritic arborization. DSPs temporally and spatially summate to reach the proximal axon where a discharge of SS is generated (Palmer et al. 2010). The DSPs are modified in amplitude and shape during their passive propagation in the dendritic tree and are also modulated by ionic-channel conductances on the PC membrane. This integration is conditioned by PCs morphology but especially by the expression of many channel types such as P/Q (Cav2.1) and T type (Cav3) $Ca^{2+}$ channels, voltage-gated $K^+$ channels (Kv1, Kv3.3) $Ca^{2+}$-activated $K^+$ channels (BK, SK) and Ih. For example, the Cav3 associated with an intermediate conductance $Ca^{2+}$-activated $K^+$ channels suppresses the temporal summation of DSPs generated by PFs activation (Engbers et al. 2012).

### *21.3.2 The Complex Spike Induced by CF Stimulation*

Stimulation of CFs results in a massive depolarization of dendrites giving rise to a CS in the soma. The CS is primarily mediated by $Na^+$ channels and in some extent by $Ca^{2+}$ channels. It consists of a large depolarization inducing one initial fast action potential followed by one to six smaller spikelets. The CS is followed by an hyperpolarization mediated by $Ca^{2+}$-activated $K^+$-channels (De Zeeuw et al. 2011). T-type

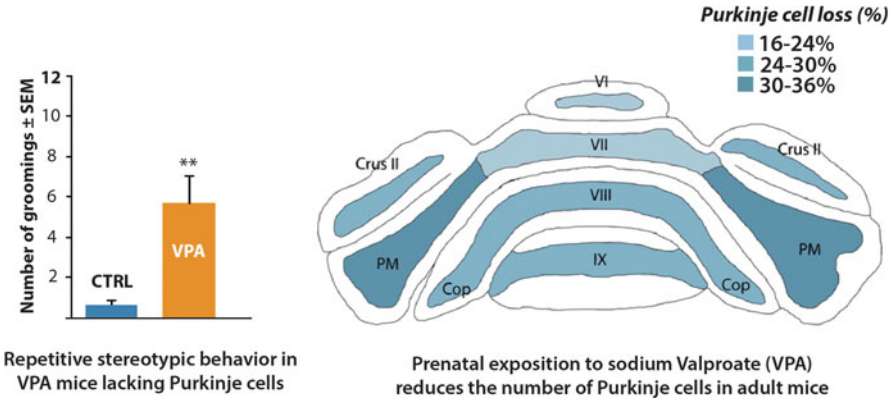


**Fig. 21.2** Repetitive stereotypic behavior (*left*) and loss of PCs (*right*) in valproate treated CD1 mice

$Ca^{2+}$ channels activated by CF stimulation participate to the CS waveform, whereas somatic Kv3.3 channels are required for spikelet generation (Kitamura and Kano 2013). The fast initial spike and the spikelets (driven by $Na^{+}$) are initiated in the initial axon (Palmer et al. 2010). Stimulation of CF also triggers dendritic $Ca^{2+}$ spikes mediated by P/Q type $Ca^{2+}$-channels. $Ca^{2+}$-spikes are not necessary for CS generation but regulate the pause in firing following the CS, probably by activating $Ca^{2+}$-dependent $K^{+}$-channels (Davie et al. 2008).

## 21.4 PCs and Autistic Syndromes

Imaging and autopsy studies of autistic patients have shown cerebellar abnormalities. Interestingly, it has been shown in mice that a PC loss is associated with autistic syndromes such as repetitive behaviors and increased activity (Martin et al. 2010). Prenatal exposition to sodium-valproate induces several autistic symptoms in mice (Roullet et al. 2013) including repetitive behaviors (Fig. 21.2, left panel). Using the autistic model of valproate-treated mice, we show a global PC loss of about 25 % (Fig. 21.2, right panel). One important challenge would be to determine how a PCs loss can induce autistic syndromes.

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