The Nodal Origin of Intrinsic Bursting

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The output of cortical neurons in the form of bursts of action potentials was thought to be controlled solely by the dendrites. In this issue of *Neuron*, Maarten Kole reveals that axonal sodium channels at the first node of Ranvier are essential for neuronal burst firing.

Patterns of action potential discharge measured in neocortical neurons in vivo are highly irregular and single spikes are often intermixed with brief bursts typically comprised of two to six action potentials with very short (usually less than 10 ms) interspike intervals. Bursts of spikes are stereotypical events. They are largely independent of the type of input stimulus and therefore constitute all-or-none units of neuronal information. In vivo, they occur spontaneously or following sensory stimulation (De Kock and Sakmann, 2008). The function of burst firing encompasses information signaling in brain circuits in normal and pathological conditions, and induction of synaptic and intrinsic plasticity underlying learning and memory. Many cortical synapses are unreliable at signaling the arrival of single presynaptic action potentials to the postsynaptic neuron. Bursts improve output reliability by facilitating transmitter release. Moreover, reliability is not only improved at the output level but also at the input side. Compared to trains of single spikes, bursts of action potentials back-propagate faithfully to distal dendrites of cortical neurons with little attenuation and initiate Ca^{2+} influx in the dendrites (Larkum et al., 1999). Furthermore, bursts of spikes can induce long-term synaptic modifications such as long-term potentiation (LTP) and depression (LTD) in cortical neurons. Finally, burst firing in pyramidal neurons can be persistently modulated following activity deprivation (Breton and Stuart, 2009), induction of status epilepticus (reviewed in Beck and Yaari, 2008) or stimulation of metabotropic glutamate receptors (Park et al., 2010).

Burst firing in cortical pyramidal neurons was widely thought to be controlled by their apical dendrites (Williams and Stuart, 1999; Larkum et al., 1999). The cellular mechanism implicated in burst generation usually involves a two-way dialog between axo-somatic and dendritic compartments that can generate mutually interacting regenerative electrical activity. Upon somatic depolarization, fast Na^+ spikes initiated in the axon back-propagate to the dendrites and produce a slow Ca^{2+} spike that returns to the axo-somatic region to trigger additional fast Na^+ spikes, thereby generating a burst of action potentials (Figure 1A). Supporting this view is the finding that local pharmacological blockade of Ca^{2+} or Na^+ channels in the dendrites of cortical neurons, or amputation of their apical dendrite, abolishes burst firing (Williams and Stuart, 1999; Bekkers and Häusser, 2007). Nevertheless, the case is not yet closed. Although electrogenesis in the dendrites appears critical for the generation of burst firing, there is also solid experimental evidence suggesting that the axonal compartment is capable of modulating sub- and suprathreshold signals generated in the dendrites. For instance, subthreshold excitatory post-synaptic potentials (EPSPs) are amplified by Na^+ channels primarily located in the proximal axon (Stuart and Sakmann, 1995; Astman et al., 2006). In addition, burst firing can still be observed in CA1 hippocampal neurons after removal of their apical dendrites (Yue et al., 2005). Thus, these studies imply that the proximal axonal region is not simply in charge of spike initiation but can also shape subthreshold potentials and perhaps determine burst firing. However, the contribution of sub-axonal compartments such as the axon initial segment (AIS) or the nodes of Ranvier (NoRs) was not established in these studies. And above all, the precise role of axonal Na^+ channels in burst firing remained unclear.

This uncertainty has been elegantly clarified in the study published in this issue of *Neuron* (Kole, 2011). Using a judicious combination of in vitro methodological approaches including targeted axotomy with two-photon illumination and local pharmacological inactivation of voltage-gated ion channels, Maarten Kole demonstrates that Na^+ channels in the first node of Ranvier (FNoR) are essential for intrinsic bursting in L5 pyramidal neurons (Figure 1B). NoRs are periodic interruptions of the myelin sheath exposing the axonal membrane to the extracellular space. They express a high density of the Nav1.6 isoform of Na^+ channels. By limiting the ionic current flow to the nodes, minimal charge is lost in the myelinated internodes, making action potential conduction fast, energy efficient, and saltatory. In L5 pyramidal neurons, the FNoR is located at ~100–120 μm from the axon hillock, which corresponds to the location of the first axonal branch point. The function of the FNoR was still controversial until very recently. Like other nodes, it could be simply mediate the propagation of the action potential from the site of initiation to the terminals. Alternatively, being located close to the cell body, the FNoR was thought to be involved in spike initiation

However, detailed analysis of spike initiation with voltage-imaging of the entire proximal segment of the axon clearly indicates that action potentials are not initiated at the FNoR but at the AIS (Popovic et al., 2011). Kole further clarifies this point by showing that the FNoR is the site of signal amplification through persistent Na^+ current that facilitates both post-spike depolarization and burst firing.

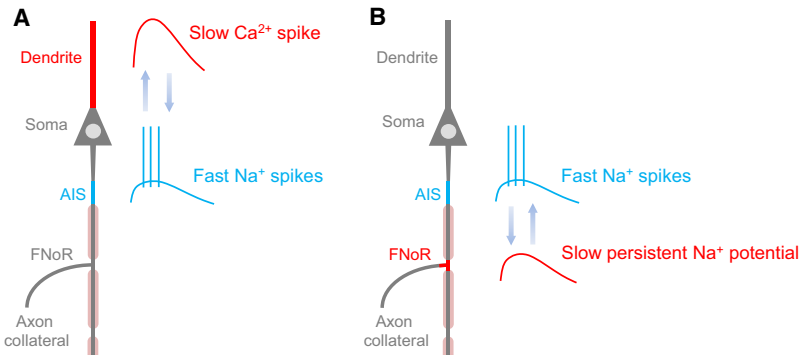

Figure 1. Two Modes of Intrinsic Bursting

(A) Burst firing generation resulting from the interplay between the apical dendrite and the AIS. Shown on the left is a schematic of a cortical pyramidal neuron with its different compartments. Depolarization of the somatic region of the neuron leads to fast Na^+ spike initiation at the AIS that back-propagates to the dendrite and generates a slow Ca^{2+} spike. At the AIS, this slow depolarizing potential generates a burst of action potentials.

(B) Burst firing generation in the axon. Depolarization of the neuron primarily causes a slow depolarizing event at the FNoR mediated by a persistent Na^+ current. At the spike trigger zone (AIS), this slow event generates a burst of action potentials.

The experiments reported in the study of Kole (2011) were conducted in an acute slice preparation of the rat neocortex, and the author observed that the firing behavior of L5 pyramidal neurons is highly correlated with the integrity of their axon after slicing. Thus, the action potential recorded in neurons with an intact axon exhibits a large after-depolarizing potential (ADP) that may eventually lead to burst firing. In contrast, spikes recorded from neurons with the axon cut proximal to the FNoR have no ADP. And neurons with a severed axon never fire in burst mode. It should be noted that the complexity of the dendritic tree does not enter into consideration here. In fact, Kole demonstrates that a given bursting neuron becomes regular if the FNoR is removed from the axon but not if the cut is made distally.

The key point of this study is that the FNoR contains a very high density of Na^+ channels that promote bursting. What is the specificity of the Na^+ channels in this region? Compared to the soma, the voltage dependence of activation and inactivation of axonal Na^+ current is shifted by 10 mV to more hyperpolarized potentials (Kole et al., 2008; Hu et al., 2009). This biophysical property has a major consequence: a larger fraction of Na^+ channels is inactivated at resting membrane potential and the relative proportion of non-inactivating (or persistent) Na^+ current is therefore larger in the axon compared to the soma. The amplitude of the persistent Na^+ current (i.e., I_{NaP}) was indeed markedly reduced in L5 axons without a first branch point (Kole, 2011), and the role of I_{NaP} is confirmed with local pharmacological agents: burst firing was abolished when Na^+ channels were pharmacologically inactivated with local application of tetrodotoxin (TTx) or solution containing zero Na^+ at the FNoR but not at the first internode.

In summary, Kole's study adds an important piece to the axon puzzle by clearly assigning a specific function to the FNoR. It further confirms that the function of the axon is not purely limited to the conduction of the action potential, but that the computational capabilities of an axon are much wider than initially thought (Debanne et al., 2011). However, all issues are not yet resolved regarding the cellular mechanisms of intrinsic bursting. If bursting primarily originates in the FNoR, what is the role of the dendrites? Are there one or two modes (Figure 1) of burst electrogenesis in pyramidal neurons? How should the experiments on dendritic inactivation/amputation be reinterpreted in light of Kole's results? These questions will certainly challenge theoreticians and experimentalists in the near future. But we can already propose that two forms of bursting may coexist in pyramidal neurons, calcium and sodium-dependent bursting that respectively depend on the somatic and axonal compartments (Figures 1A and 1B). In fact, these two forms of bursting share a common feature: the need for a slow depolarizing event generated outside the site of spike initiation but electrically coupled to it.

The results reported by Kole are not only important because they allow a better understanding of the elementary mechanisms underlying intrinsic bursting. They also raise the critical issue that the mechanisms of activity-dependent regulation of burst firing in pyramidal neurons must be reconsidered. Usually attributed to the dendrites, this form of plasticity may in fact involve the axon and more specifically the FNoR. It can be expected that these findings will spur us on to determine the contribution of the FNoR to plasticity of intrinsic bursting.

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