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Signal propagation along the axon

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Axons link distant brain regions and are usually considered as simple transmission cables in which reliable propagation occurs once an action potential has been generated. Safe propagation of action potentials relies on specific ion channel expression at strategic points of the axon such as nodes of Ranvier or axonal branch points. However, while action potentials are generally considered as the quantum of neuronal information, their signaling is not entirely digital. In fact, both their shape and their conduction speed have been shown to be modulated by activity, leading to regulations of synaptic latency and synaptic strength. We report here newly identified mechanisms of (1) safe spike propagation along the axon, (2) compartmentalization of action potential shape in the axon, (3) analog modulation of spike-evoked synaptic transmission and (4) alteration in conduction time after persistent regulation of axon morphology in central neurons. We discuss the contribution of these regulations in information processing.

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Introduction: axonal propagation, information signaling and timing

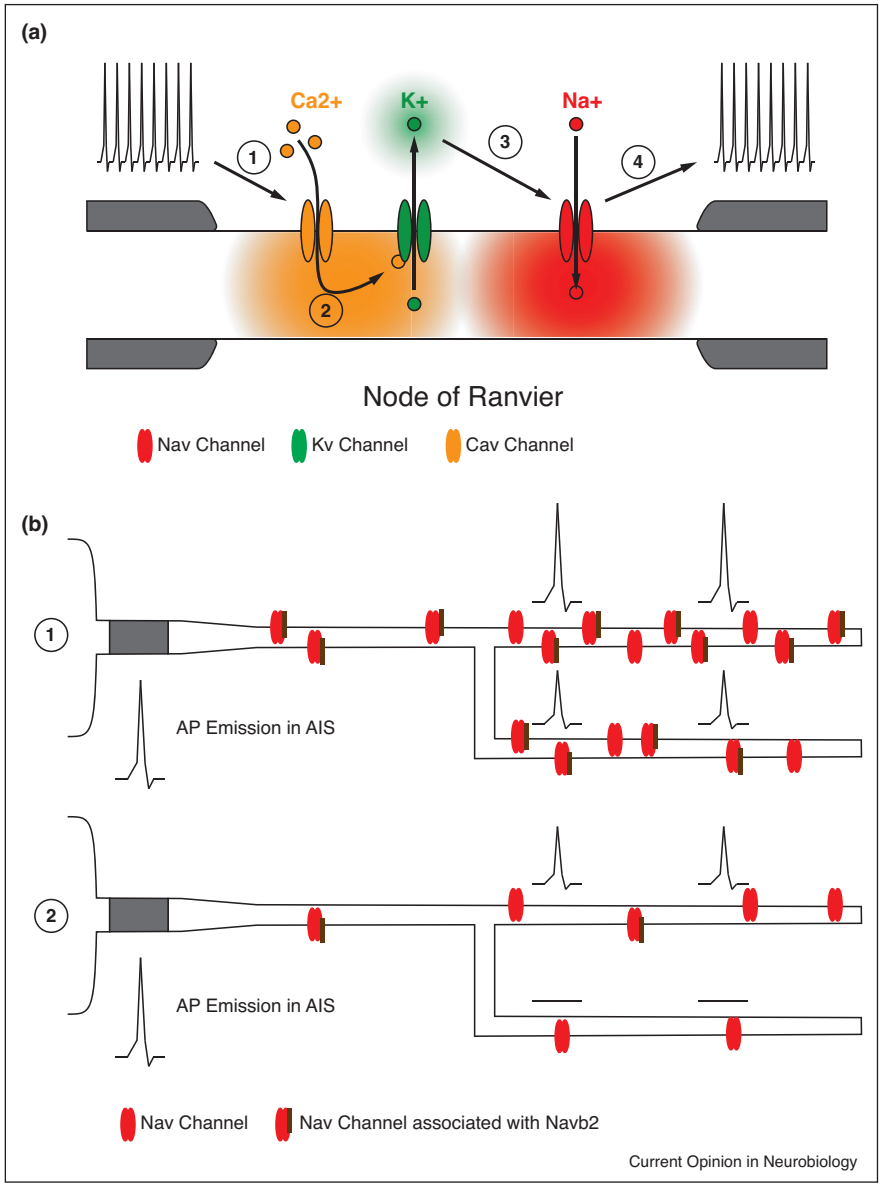
For ages, the axon has been considered as a neuronal process that insures the conduction of neuronal information from the site of initiation near the cell body to the presynaptic terminals. Nevertheless, recent findings indicate that the axon function is not reduced to the sole conduction of the action potential and experimental data reported these last years have identified new mechanisms that enlarge functional and computational repertoire of axons. We will first review recent findings about new mechanisms controlling faithful action potential propagation at axonal branch points and node of Ranvier. Second, we will describe recent studies indicating that action potential waveform is compartmentalized in the different segments of the axon. Then, we will show that the shape of the action potential in the axon can influence transmission of information at the output side, thus producing an analog-digital form of signaling. Finally, we will discuss recent data reporting activity-dependent plasticity of axon morphology and excitability. We will highlight the functional consequences of these newly identified mechanisms by showing how they affect axon function by finely tuning the output message and spike conduction time in brain circuits.

Factors controlling action potential propagation

According to the classical view of signal propagation in the axon, once generated spikes are propagated faithfully to the presynaptic terminal. In many types of axon, however, repetitive stimulation at medium to high frequency (10–50 Hz) has been shown to result in conduction failures occurring specifically at branch points [1]. Beyond the geometrical perturbation that constitutes per se a low safety conduction point, the main mechanisms lie in the activity dependent depolarization of the axon membrane by a few millivolts mediated by accumulation of K^+ ions in the extracellular space that in turn leads to sodium channel inactivation and propagation failure [2,3]. Axons of cerebellar Purkinje cells (PC) display a much higher cutting frequency (i.e. critical frequency of stimulation at which conduction failures occur) since failures at the first branch point of PC axons generally occur at frequencies above 200–250 Hz [4,5]. Although the high frequency firing in PC cell is due to the presence of resurgent Na^+ current [6,7] that shortens the refractory period, the relatively high threshold for failures of action potential propagation along the axon results from the presence of calcium-activated potassium channels of intermediate conductance ($K_{Ca}3.1$) in the axon [8••]. In this study, Grundemann and Clark showed using a combination of electrophysiological recordings from the axon, calcium imaging, pharmacology and modeling that local activity-dependent calcium influx at nodes of Ranvier recruits $K_{Ca}3.1$ that subsequently hyperpolarizes membrane potential, promotes Na^+ channel availability and secures spike propagation (Figure 1a).

A second mechanism for securing spike propagation has been identified more recently in axons of hippocampal cells. Voltage-gated Na^+ channel subunits (Nav) are critical drivers for active conduction along the axon and a deficit in the expression of Nav channels at the plasma

Figure 1



New mechanisms ensuring spikes propagation along the axon. **(a)** $K_{Ca}3.1$ channels activation avoids conduction failures in Purkinje cells nodes of Ranvier. (1) High frequency spike trains activate low threshold Ca^{2+} current (It). (2) Rise of intracellular Ca^{2+} concentration activates calcium-dependent $K_{Ca}3.1$ leading to (3) repolarization of membrane potential and de-inactivation of Nav. (4) Nav channels availability allows faithful propagation of spike trains. Adapted from [8••]. **(b)** Navβ2 subunit is a major determinant of axonal branches excitability in cortical cells. (1) In control condition, some axonal branches display a high level of Navβ2 leading to a high Nav channels membrane expression and large spike amplitude (upper branch). A low Navβ2 expression entails a weak Nav channels membrane expression and smaller spikes (lower branch). (2) After Navβ2 knock-down, conduction failures appear at branch points, caused by the decrease in Nav channels membrane expression. Adapted from [10••].

membrane may thus destabilize spike propagation. In the brain, pore-forming Nav α-subunits (Nav-α) are generally associated with transmembrane regulatory β-subunits. Na^+ channel β2 (or Nav-β2) subunits have been shown to regulate membrane trafficking of Nav-α. The lack of Nav-β2 reduces by half the amplitude of sodium currents [9]. Yet, the consequences of the Nav-β2 depletion on spike propagation had not been yet evaluated experimentally. The recent study by the group of Michael Hoppa filled this gap by showing with the use of genetically-encoded voltage-imaging combined with calcium imaging that genetic deletion of Nav-β2 induces collateral-selective propagation failures in axons of hippocampal cells [10••] (Figure 1b).