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## Signal propagation along the axon

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Abstract:

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.

### ***Introduction: axonal propagation, information signaling & 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 illustrate novel modes of information processing in the axon (analog-digital 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<sup>+</sup> 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]. While the high frequency firing in PC cell is due to the presence of resurgent Na<sup>+</sup> 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<sub>Ca</sub>3.1) in the axon [8]. In this study, Grundemann & 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<sub>Ca</sub>3.1 that subsequently hyperpolarizes membrane potential, promotes Na<sup>+</sup> 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<sup>+</sup> channel subunits (Nav) are critical drivers for active

conduction along the axon and a deficit in the expression of Nav channels at the plasma membrane may thus destabilize spike propagation. In the brain, pore-forming Nav  $\alpha$ -subunits (Nav- $\alpha$ ) are generally associated with transmembrane regulatory  $\beta$ -subunits. Na<sup>+</sup> channel  $\beta$ 2 (or Nav- $\beta$ 2) subunits have been shown to regulate membrane trafficking of Nav- $\alpha$ . The lack of Nav- $\beta$ 2 reduces by half the amplitude of sodium currents [9]. Yet, the consequences of the Nav- $\beta$ 2 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- $\beta$ 2 induces collateral-selective propagation failures in axons of hippocampal cells [10] (**Figure 1B**).

### ***Compartmentalization of action potential waveform in the axon***

While axons are tuned to insure action potential propagation all along the axon, the shape of the signal is locally altered during this process. In fact, recent experimental works tend to demonstrate that ion channels present in the axon display a highly heterogeneous distribution among axonal branches. As the action potential is locally shaped by voltage-dependent channels, a compartmentalized distribution of ion channels leads to branch-dependent (or even terminal-dependent) modulation of spike shape. In cerebellar stellate cell interneurons, action potential width and the resultant GABA release is determined by the local density of Kv3 channels found at each terminal [11]. In a similar way, differential expression of Nav $\beta$ 2 subunits induces heterogeneous action potential amplitudes in various hippocampal axonal branches [10]. Moreover, expression of Kv7 at nodes of Ranvier in neocortical pyramidal cells strongly hyperpolarizes the membrane potential and thus improves Nav channel availability and optimal spike amplitude [12]. Therefore, action potential shape is locally determined by ions channel distribution all along the axon possibly leading to variations in neurotransmitter release in axonal compartments.

### ***Analog-digital signaling in the axon***

Signaling in central neurons is classically based on spike-evoked transmission of packets of neurotransmitter in a digital (or all-or-none) manner. Increasing evidence shows, however, that the shape of the presynaptic action potential can be modulated which in turn modifies the neurotransmitter release. It led to the emergence of the concept of hybrid Analog-Digital modulation of synaptic transmission in mammalian axons, in which the shape of the action potential is modulated by the analog context in which it is triggered [13-16]. Moreover, the presynaptic voltage-gated Ca<sup>2+</sup> channels (Cav) opening is steeply dependent on action potential waveform [17] and, at both glutamatergic and GABAergic terminals, vesicle fusion is supralinearly dependent on Ca<sup>2+</sup> entry [18,19]. Therefore, the spike shape can exert a strong impact on neurotransmission [20].

It has been shown that sub-threshold membrane potential fluctuations of the cell body are electrically transmitted by the axon over hundreds of micrometers to the terminals where they modulate the AP waveform [15,21,22]. Long depolarization of the membrane potential (0.2-10 s to -50 mV) has been shown to inactivate presynaptic Kv1 channels leading to action potential broadening and increase in neurotransmitters release in cortical [23-25], and hippocampal pyramidal neurons [26-28] (**Figure 2A**). This analog-digital facilitation induced by depolarization (d-ADF) is not exclusively observed in glutamate-releasing neurons but it is also seen on GABA-releasing interneurons. In this case, the mechanism depends either on spike-waveform through presynaptic Kv3.4 [29] or on the increase in basal calcium during subthreshold depolarization via activation of P/Q type calcium channels [30,31]. Modulation of basal calcium concentration by presynaptic membrane potential is also the main mechanism of d-ADF in auditory neurons [32,33], mitral cells of the olfactory bulb [34] and sensory neurons of the Aplysia [35]. However, in granule cells of the dentate gyrus, the mechanism of d-ADF remains unknown [18,36].

Analog modulation of synaptic transmission by changes in presynaptic membrane potential is not restricted to K<sup>+</sup> and Ca<sup>2+</sup> channels but may also affect voltage-gated Na<sup>+</sup> (Nav) channels. A large proportion of the Nav current in the axon and presynaptic terminal is inactivated at rest. In fact, while ~20% of the Nav current is inactivated in the soma [37], ~70% of the Nav current is inactivated in axons of cortical and hippocampal neurons [37-39]. The consequence of this strong Nav channel inactivation in the axon is a large modulation of the amplitude of the axonal action potential during changes in membrane potential [40]. We showed that transient hyperpolarization in the soma of the presynaptic cell (15-200 ms at -80 mV) enhanced the amplitude of the action potential recorded in the axon, and thus augmented both presynaptic calcium influx and glutamate release (**Figure 2B**). This hyperpolarization-induced Analog-Digital Facilitation (h-ADF) can be induced by synaptic inhibition and is likely to promote network synchrony at gamma frequency [40].

The modulation of the spike waveform is not limited to the physiological context and dysfunctions of Kv1 channels have been reported in rodent models of schizophrenia [41], episodic ataxia type 1 [42,43] and epilepsy [44]. This dysfunction in Kv1 channel usually results in increased excitability [41,44,45], broadening of axonal spike width [42] and increased synaptic transmission [42,44].

Modulation of spike-evoked synaptic transmission may also result from activation of ligand-gated receptors located on presynaptic terminals. Local activation of AMPA-type glutamate receptors on CA3 pyramidal axons has been shown to broaden the action potential and increase synaptic transmission [46]. In a similar way, GABA released by cerebellar interneurons or by Purkinje cells has been shown to depolarize their axon terminals locally [47] and this depolarization associated with incoming action potentials promote GABA release [19]. GABA also exerts specific action on

presynaptic terminals in glutamatergic neurons. In the mossy fiber bouton, presynaptic GABA<sub>A</sub> receptors activation depolarizes the terminal leading to AP broadening and enhancement of AP-dependent Ca<sup>2+</sup> entry [48-50]. On the contrary, the shunting effect of GABA<sub>A</sub> receptors activation in L5 pyramidal neurons provokes a reduction of spike width and spike evoked Ca<sup>2+</sup> entry [51]. In conclusion, spike waveform is a major determinant of neuronal output message. Its modulation occurs in physiological and pathological contexts.

### ***Activity-dependent plasticity of action potential propagation***

Besides spike waveform modulation, other axonal parameters can be regulated. In fact, following manipulation of neuronal activity, conduction velocity and axonal excitability have also been shown to be modulated. The most important functional property of the axon is the conduction of the action potential. Conduction velocity depends on 3 factors: morphology (axon diameter), myelin insulation (width of myelin and internode length), and ion channel density (mainly Nav and Kv channels). Action potential propagation is subject to activity-dependent plasticity and axon stimulation produces short- and long-term modulation in action potential conduction. Low frequency stimulation (1 - 20 Hz) of granule cell axons has been shown to result in a transient decrease in action potential conduction velocity [52]. The long-term effect of repetitive axonal stimulation on action potential propagation has been very recently analyzed with the use of super-resolution imaging techniques. LTP induced in the CA1 region by high frequency stimulation of the Schaffer collateral has been shown to produce a persistent increase in both axon and synaptic bouton diameter [53]. These enlargements of axon and bouton diameter reach on average ~5% and are NMDA receptor-dependent. Importantly, these morphological changes differentially affect conduction velocity. In fact, conduction velocity of the Schaffer collateral after LTP induction was found to be transiently decreased because of the transient enlargement of the synaptic boutons and then increased as the result of enlargement of the diameter of the axon shaft (**Figure 3**). It is important to note that the advance in spike conduction delay after LTP induction is entirely coherent with the advance in synaptic delay observed following LTP induction in cortical cell pairs [54]. While the two phenomena involve different mechanisms – changes in axon diameter in one case and release-dependent variations in the other case – it is striking to notice that both enter in a general framework where synaptic potentiation shortens neuronal time delay. Although the changes in spike conduction reported in the study by the group of Valentin Nägerl are entirely predicted by morphological changes [53], one cannot exclude the contribution of other mechanisms such as axo-glial interactions [55]. In fact, depolarization of a single oligodendrocyte increases conduction velocity in hippocampal axons [56]. Furthermore, active axons favor myelination during development through axonal release of glutamate [57,58]. In addition, axon geometry has been shown to be finely tuned to match functional properties. Auditory

brainstem neurons analyze a wide range of sound frequency and function as devices analyzing temporal processing. In this neurons, axons are myelinated and interestingly, the geometry of their nodes of Ranvier and their internodes is tuned to optimally adjust action potential timing [59].

Beyond conduction, axonal excitability has also been shown to be modulated by activity. The first evidence for persistent plasticity of axonal excitability has been published more than 20 years ago and showed that repetitive stimulation of Schaffer collateral axons at 2 Hz led to a long-lasting reduction of the activation threshold of the axon [60]. Although the precise expression mechanisms have not been characterized here, this study suggests that axonal excitability is persistently enhanced if the axon is repetitively stimulated. A more recent study has reported a novel form of activity-dependent plasticity in a subclass of inhibitory interneurons of the cortex and hippocampus containing neuropeptide Y [61]. It was shown in this study that stimulation of the interneuron at 20–40 Hz led to enhanced action potential firing lasting several minutes. This persistent firing is consistent with the development of an ectopic spike initiation zone in the distal region of the axon.

### ***Conclusion & future directions***

The recent progress in axon physiology reported in this review have been made possible by the development of cutting edge techniques as imaging of membrane potential with genetically-encoded voltage indicators [10,62], patch-clamp recording from thin axons [24,25,40,63,64] and super-resolution confocal microscopy [53]. What further progress can be expected in the nearest future? There are at least two important breakthrough that can be considered. First, regarding analog-digital processing, future investigation should be conducted to examine its implication in coding of neuronal information [16]. Second, important discoveries can be envisaged in the context of activity-dependent plasticity of axon function. In fact, while activity-dependent regulation of the composition of axon initial segment has been intensively studied [65-69], the consequences of homeostatic regulation of ion channels distribution on other axonal properties should be seriously envisaged in the future since many ion channels that determine functional properties in the axon also undergo homeostatic plasticity [70-72]. The future will probably tell us more about axon function.

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### **Figure 1. New mechanisms ensuring spikes propagation along the axon.**

**A.**  $K_{Ca3.1}$  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  $K_{Ca3.1}$  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.** Nav $\beta$ 2 subunit is a major determinant of axonal branches excitability in cortical cells. 1) In control condition, some axonal branches display a high level of Nav $\beta$ 2 leading to a high Nav channels membrane expression and large spike amplitude (upper branch). A low Nav $\beta$ 2 expression entails a weak Nav channels membrane expression and smaller spikes (lower branch). 2) After Nav $\beta$ 2 knock-down, conduction failures appear at branch points, caused by the decrease in Nav channels membrane expression. Adapted from [10].

**Figure 2. Axonal sodium and potassium channels modulate spike shape and release probability.**

**A.** Top, at resting potential, Kv1 channels are available and insure a quick recovery of depolarization during AP conduction. The resulting AP is thin, producing a moderate calcium entry in the presynaptic bouton and neurotransmitter release. Bottom, when the neuron is depolarized for a long period of time ( $\tau=3.7s$ ), Kv1 channels are inactivated and thus produce a broad AP. This increases calcium entry in the presynaptic element and the resulting neurotransmitter release. Adapted from [26]. **B.** Top, at resting potential, axonal sodium channels are mainly inactivated and in consequence, APs are short. Bottom, when briefly hyperpolarized ( $15\text{ ms} < t < 200\text{ ms}$ ), sodium channels recover from inactivation and thus produce an AP of greater amplitude. The resulting calcium entry is increased, as is the neurotransmitter release. Adapted from [40].

**Figure 3. Long-lasting regulation of action potential conduction delay.** Left, action potential timing before the high frequency stimulation of the axon. Middle, delayed spike conduction caused by the short-term enlargement of synaptic boutons. Right, long-lasting increase in conduction velocity caused by the enlargement of the axon diameter. Adapted from [53].

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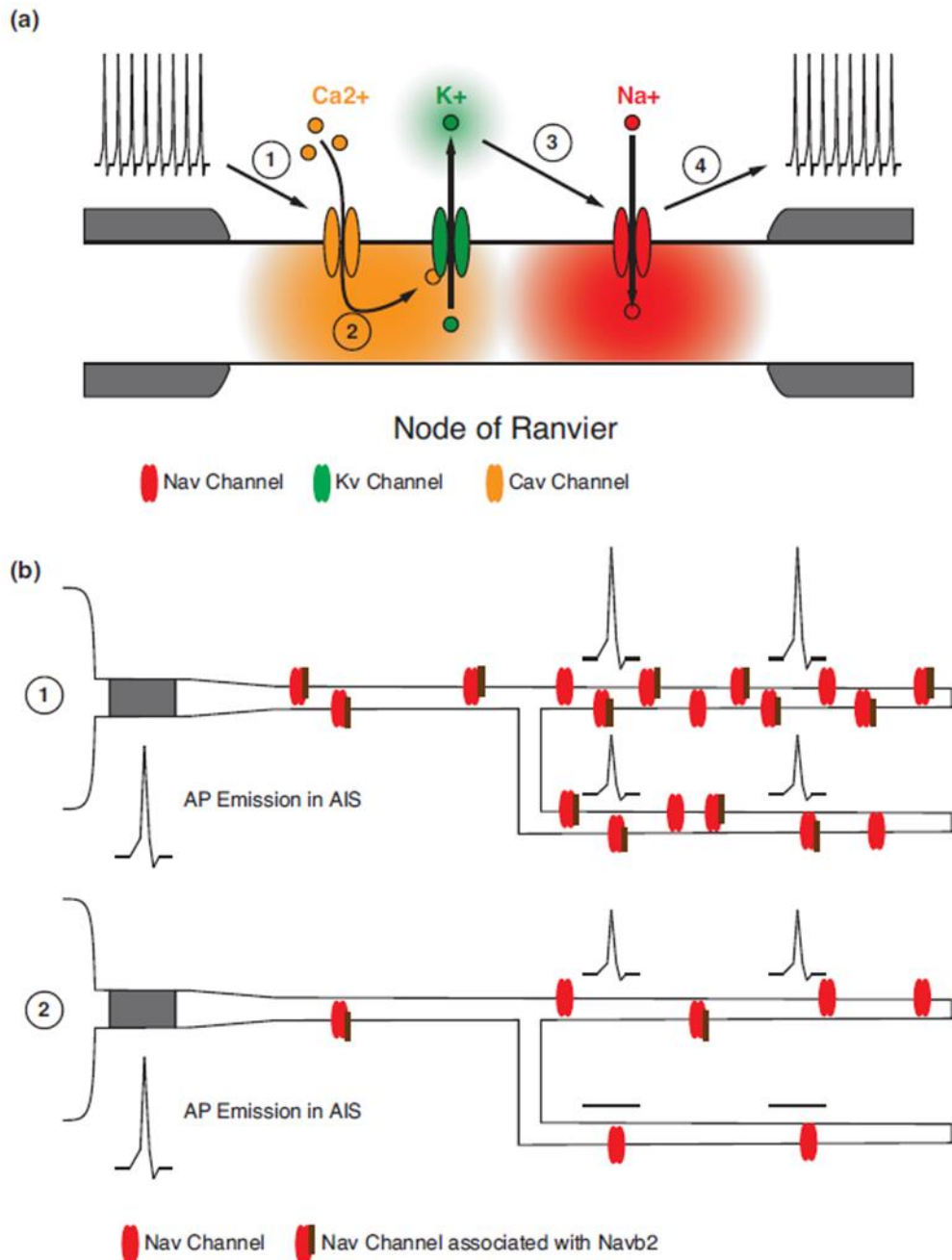
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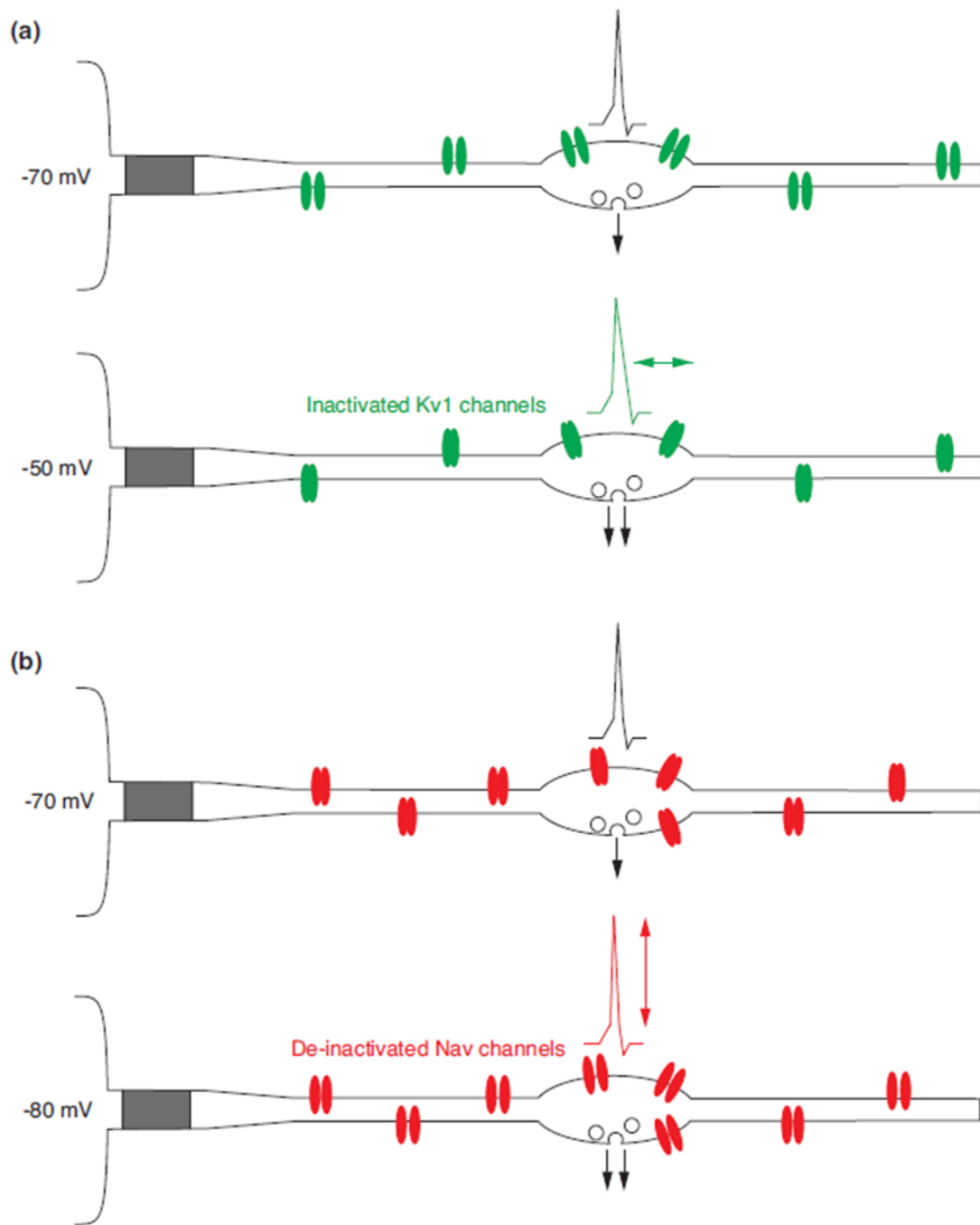
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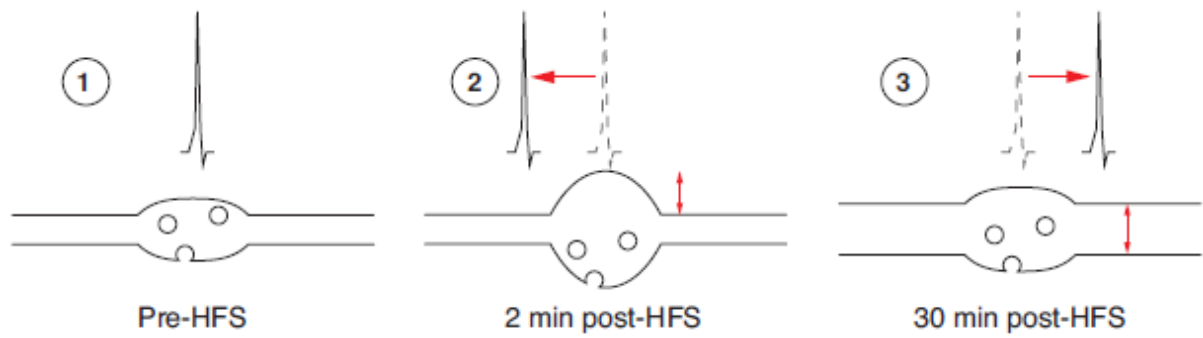
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**Figure 1. New mechanisms ensuring spikes propagation along the axon.** (a) KCa3.1 channels activation avoids conduction failures in Purkinje cells nodes of Ranvier. (1) High frequency spike trains activate low threshold  $\text{Ca}^{2+}$  current ( $I_t$ ). (2) Rise of intracellular  $\text{Ca}^{2+}$  concentration activates calciumdependent KCa3.1 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) Navb2 subunit is a major determinant of axonal branches excitability in cortical cells. (1) In control condition, some axonal branches display a high level of Navb2 leading to a high Nav channels membrane expression and large spike amplitude (upper branch). A low Navb2 expression entails a weak Nav channels membrane expression and smaller spikes (lower branch). (2) After Navb2 knock down, conduction failures appear at branch points, caused by the decrease in Nav channels membrane expression. Adapted from [10].



**Figure 2. Axonal sodium and potassium channels modulate spike shape and release probability.** (a) Top, at resting potential, Kv1 channels are available and insure a quick recovery of depolarization during AP conduction. The resulting AP is thin, producing a moderate calcium entry in the presynaptic bouton and neurotransmitter release. Bottom, when the neuron is depolarized for a long period of time ( $t = 3.7$  s), Kv1 channels are inactivated and thus produce a broad AP. This increases calcium entry in the presynaptic element and the resulting neurotransmitter release. Adapted from [26]. (b) Top, at resting potential, axonal sodium channels are mainly inactivated and in consequence, APs are short. Bottom, when briefly hyperpolarized ( $15 \text{ ms} < t < 200 \text{ ms}$ ), sodium channels recover from inactivation and thus produce an AP of greater amplitude. The resulting calcium entry is increased, as is the neurotransmitter release. Adapted from [40].



**Figure 3. Long-lasting regulation of action potential conduction delay.** Left, action potential timing before the high frequency stimulation of the axon. Middle, delayed spike conduction caused by the short-term enlargement of synaptic boutons. Right, long-lasting increase in conduction velocity caused by the enlargement of the axon diameter. Adapted from [53].