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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^+ 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^+ 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 ($K_{Ca3.1}$) 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 $K_{Ca3.1}$ 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 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 β 2 (or Nav- β 2) subunits have been shown to regulate membrane trafficking of Nav- α . The lack of Nav- β 2 reduces by half the amplitude of sodium currents [9]. Yet, the consequences of the Nav- β 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- β 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 tune 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 β 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 Ca²⁺ channels (Cav) opening is steeply dependent on action potential waveform [17] and, at both glutamatergic and GABAergic terminals, vesicle fusion is supralinearly dependent on Ca²⁺ 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^+ and Ca^{2+} channels but may also affect voltage-gated Na^+ (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_A receptors activation depolarizes the terminal leading to AP broadening and enhancement of AP-dependent Ca²⁺ entry [48-50]. On the contrary, the shunting effect of GABA_A receptors activation in L5 pyramidal neurons provokes a reduction of spike width and spike evoked Ca²⁺ 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 β 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 β 2 leading to a high Nav channels membrane expression and large spike amplitude (upper branch). A low Nav β 2 expression entails a weak Nav channels membrane expression and smaller spikes (lower branch). 2) After Nav β 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].

References

- of special interest:
- 11. Rowan et al., 2016. This study shows that action potential width is not uniform across the axon arbor of cerebellar interneurons.
- 19. Zorrilla de San Martin et al., 2017. This paper shows how the depolarization of presynaptic GABA $_A$ receptors facilitates synaptic transmission in Purkinje cells.
- 26. Bialowas et al., 2015. This study shows how long presynaptic depolarization increases spike duration and postsynaptic response in CA3 pyramidal neurons.

29. Rowan & Christie, 2017. This paper points the role of Kv3.4 channels in depolarization-dependent facilitation of GABA release in cerebellar interneurons.

46. Sasaki & Ikegaya, 2011. This study reveals that activation of astrocyte broadens the spike in the axon and increase postsynaptic response.

59. Ford et al., 2015. This paper shows that the geometry of the node of Ranvier and internodes in neurons of the auditory tract is tuned to optimally adjust action potential timing.

61. Sheffield et al., 2011. This paper shows that stimulation of cortical interneurons at 20–40 Hz leads to increased action potential firing lasting several minutes.

•• of outstanding interest:

8. Grundemann & Clark, 2015. This study identifies $K_{Ca3.1}$ channels at nodes of Ranvier as a key determinant for safe conduction in axons of Purkinje cell.

10. Cho et al., 2017. This paper shows using genetically encoded voltage and calcium indicators that repression of Nav β 2 subunits leads to failures of action potential conduction in axon branches.

40. Rama et al., 2015. This study shows that hyperpolarization preceding presynaptic spike by a few tens of milliseconds increases spike amplitude in pyramidal cell axons and amplitude of post-synaptic response.

53. Chéreau et al., 2017. This study shows using super-resolution microscopy that long-term potentiation is associated with an increase in axon diameter that in turn augments action potential conduction velocity.

1. Debanne D: **Information processing in the axon.** *Nat Rev Neurosci* 2004, **5**:304-316.
2. Grossman Y, Parnas I, Spira ME: **Differential conduction block in branches of a bifurcating axon.** *J Physiol* 1979, **295**:283-305.
3. Grossman Y, Parnas I, Spira ME: **Mechanisms involved in differential conduction of potentials at high frequency in a branching axon.** *J Physiol* 1979, **295**:307-322.
4. Monsivais P, Clark BA, Roth A, Hausser M: **Determinants of action potential propagation in cerebellar Purkinje cell axons.** *J Neurosci* 2005, **25**:464-472.
5. Khaliq ZM, Raman IM: **Axonal propagation of simple and complex spikes in cerebellar Purkinje neurons.** *J Neurosci* 2005, **25**:454-463.
6. Raman IM, Bean BP: **Resurgent sodium current and action potential formation in dissociated cerebellar Purkinje neurons.** *J Neurosci* 1997, **17**:4517-4526.
7. Lewis AH, Raman IM: **Resurgent current of voltage-gated Na(+) channels.** *J Physiol* 2014, **592**:4825-4838.
8. Grundemann J, Clark BA: **Calcium-Activated Potassium Channels at Nodes of Ranvier Secure Axonal Spike Propagation.** *Cell Rep* 2015, **12**:1715-1722.
9. Chen C, Bharucha V, Chen Y, Westenbroek RE, Brown A, Malhotra JD, Jones D, Avery C, Gillespie PJ, 3rd, Kazen-Gillespie KA, et al.: **Reduced sodium channel density, altered voltage dependence of inactivation, and increased susceptibility to seizures in mice lacking sodium channel beta 2-subunits.** *Proc Natl Acad Sci U S A* 2002, **99**:17072-17077.
10. Cho IH, Panzera LC, Chin M, Hoppa MB: **Sodium Channel beta2 Subunits Prevent Action Potential Propagation Failures at Axonal Branch Points.** *J Neurosci* 2017, **37**:9519-9533.
11. Rowan MJ, DelCanto G, Yu JJ, Kamasawa N, Christie JM: **Synapse-Level Determination of Action Potential Duration by K(+) Channel Clustering in Axons.** *Neuron* 2016, **91**:370-383.

12. Battefeld A, Tran BT, Gavrilis J, Cooper EC, Kole MH: **Heteromeric Kv7.2/7.3 channels differentially regulate action potential initiation and conduction in neocortical myelinated axons.** *J Neurosci* 2014, **34**:3719-3732.
13. Alle H, Geiger JR: **Analog signalling in mammalian cortical axons.** *Curr Opin Neurobiol* 2008, **18**:314-320.
14. Clark B, Hausser M: **Neural coding: hybrid analog and digital signalling in axons.** *Curr Biol* 2006, **16**:R585-588.
15. Debanne D, Bialowas A, Rama S: **What are the mechanisms for analogue and digital signalling in the brain?** *Nat Rev Neurosci* 2013, **14**:63-69.
16. Juusola M, Robinson HP, de Polavieja GG: **Coding with spike shapes and graded potentials in cortical networks.** *Bioessays* 2007, **29**:178-187.
17. Bischofberger J, Geiger JR, Jonas P: **Timing and efficacy of Ca²⁺ channel activation in hippocampal mossy fiber boutons.** *J Neurosci* 2002, **22**:10593-10602.
18. Scott R, Ruiz A, Henneberger C, Kullmann DM, Rusakov DA: **Analog modulation of mossy fiber transmission is uncoupled from changes in presynaptic Ca²⁺.** *J Neurosci* 2008, **28**:7765-7773.
19. Zorrilla de San Martin J, Trigo FF, Kawaguchi SY: **Axonal GABAA receptors depolarize presynaptic terminals and facilitate transmitter release in cerebellar Purkinje cells.** *J Physiol* 2017.
20. Geiger JR, Jonas P: **Dynamic control of presynaptic Ca(2+) inflow by fast-inactivating K(+) channels in hippocampal mossy fiber boutons.** *Neuron* 2000, **28**:927-939.
21. Rama S, Zbili M, Debanne D: **Modulation of spike-evoked synaptic transmission: The role of presynaptic calcium and potassium channels.** *Biochim Biophys Acta* 2015, **1853**:1933-1939.
22. Zbili M, Rama S, Debanne D: **Dynamic Control of Neurotransmitter Release by Presynaptic Potential.** *Front Cell Neurosci* 2016, **10**:278.
23. Foust AJ, Yu Y, Popovic M, Zecevic D, McCormick DA: **Somatic membrane potential and Kv1 channels control spike repolarization in cortical axon collaterals and presynaptic boutons.** *J Neurosci* 2011, **31**:15490-15498.
24. Kole MH, Letzkus JJ, Stuart GJ: **Axon initial segment Kv1 channels control axonal action potential waveform and synaptic efficacy.** *Neuron* 2007, **55**:633-647.
25. Shu Y, Hasenstaub A, Duque A, Yu Y, McCormick DA: **Modulation of intracortical synaptic potentials by presynaptic somatic membrane potential.** *Nature* 2006, **441**:761-765.
26. Bialowas A, Rama S, Zbili M, Marra V, Fronzaroli-Molinieres L, Ankri N, Carlier E, Debanne D: **Analog modulation of spike-evoked transmission in CA3 circuits is determined by axonal Kv1.1 channels in a time-dependent manner.** *Eur J Neurosci* 2015, **41**:293-304.
27. Kim S: **Action Potential Modulation in CA1 Pyramidal Neuron Axons Facilitates OLM Interneuron Activation in Recurrent Inhibitory Microcircuits of Rat Hippocampus.** *PLoS One* 2014, **9**:e113124.
28. Sasaki T, Matsuki N, Ikegaya Y: **Effects of axonal topology on the somatic modulation of synaptic outputs.** *J Neurosci* 2012, **32**:2868-2876.
29. Rowan MJ, Christie JM: **Rapid State-Dependent Alteration in Kv3 Channel Availability Drives Flexible Synaptic Signaling Dependent on Somatic Subthreshold Depolarization.** *Cell Rep* 2017, **18**:2018-2029.
30. Bouhours B, Trigo FF, Marty A: **Somatic depolarization enhances GABA release in cerebellar interneurons via a calcium/protein kinase C pathway.** *J Neurosci* 2011, **31**:5804-5815.
31. Christie JM, Chiu DN, Jahr CE: **Ca(2+)-dependent enhancement of release by subthreshold somatic depolarization.** *Nat Neurosci* 2011, **14**:62-68.
32. Awatramani GB, Price GD, Trussell LO: **Modulation of transmitter release by presynaptic resting potential and background calcium levels.** *Neuron* 2005, **48**:109-121.
33. Hori T, Takahashi T: **Mechanisms underlying short-term modulation of transmitter release by presynaptic depolarization.** *J Physiol* 2009, **587**:2987-3000.

34. Fekete A, Johnston J, Delaney KR: **Presynaptic T-type Ca²⁺ channels modulate dendrodendritic mitral-mitral and mitral-periglomerular connections in mouse olfactory bulb.** *J Neurosci* 2014, **34**:14032-14045.
35. Ludwar BC, Evans CG, Cambi M, Cropper EC: **Activity-dependent increases in [Ca²⁺]_i contribute to digital-analog plasticity at a molluscan synapse.** *J Neurophysiol* 2017, **117**:2104-2112.
36. Alle H, Geiger JR: **Combined analog and action potential coding in hippocampal mossy fibers.** *Science* 2006, **311**:1290-1293.
37. Hu W, Tian C, Li T, Yang M, Hou H, Shu Y: **Distinct contributions of Na(v)1.6 and Na(v)1.2 in action potential initiation and backpropagation.** *Nat Neurosci* 2009, **12**:996-1002.
38. Engel D, Jonas P: **Presynaptic action potential amplification by voltage-gated Na⁺ channels in hippocampal mossy fiber boutons.** *Neuron* 2005, **45**:405-417.
39. Schmidt-Hieber C, Bischofberger J: **Fast sodium channel gating supports localized and efficient axonal action potential initiation.** *J Neurosci* 2010, **30**:10233-10242.
40. Rama S, Zbili M, Bialowas A, Fronzaroli-Molinieres L, Ankri N, Carlier E, Marra V, Debanne D: **Presynaptic hyperpolarization induces a fast analogue modulation of spike-evoked transmission mediated by axonal sodium channels.** *Nat Commun* 2015, **6**:10163.
41. Crabtree GW, Sun Z, Kvajo M, Broek JA, Fenelon K, McKellar H, Xiao L, Xu B, Bahn S, O'Donnell JM, et al.: **Alteration of Neuronal Excitability and Short-Term Synaptic Plasticity in the Prefrontal Cortex of a Mouse Model of Mental Illness.** *J Neurosci* 2017, **37**:4158-4180.
42. Begum R, Bakiri Y, Volynski KE, Kullmann DM: **Action potential broadening in a presynaptic channelopathy.** *Nat Commun* 2016, **7**:12102.
43. Vivekananda U, Novak P, Bello OD, Korchev YE, Krishnakumar SS, Volynski KE, Kullmann DM: **Kv1.1 channelopathy abolishes presynaptic spike width modulation by subthreshold somatic depolarization.** *Proc Natl Acad Sci U S A* 2017, **114**:2395-2400.
44. Seagar M, Russier M, Caillard O, Maulet Y, Fronzaroli-Molinieres L, De San Feliciano M, Boumedine-Guignon N, Rodriguez L, Zbili M, Usseglio F, et al.: **LGI1 tunes intrinsic excitability by regulating the density of axonal Kv1 channels.** *Proc Natl Acad Sci U S A* 2017, **114**:7719-7724.
45. Rama S, Zbili M, Fekete A, Tapia M, Benitez MJ, Boumedine N, Garrido JJ, Debanne D: **The role of axonal Kv1 channels in CA3 pyramidal cell excitability.** *Sci Rep* 2017, **7**:315.
46. Sasaki T, Matsuki N, Ikegaya Y: **Action-potential modulation during axonal conduction.** *Science* 2011, **331**:599-601.
47. Trigo FF, Chat M, Marty A: **Enhancement of GABA release through endogenous activation of axonal GABA(A) receptors in juvenile cerebellum.** *J Neurosci* 2007, **27**:12452-12463.
48. Ruiz A, Fabian-Fine R, Scott R, Walker MC, Rusakov DA, Kullmann DM: **GABAA receptors at hippocampal mossy fibers.** *Neuron* 2003, **39**:961-973.
49. Alle H, Geiger JR: **GABAergic spill-over transmission onto hippocampal mossy fiber boutons.** *J Neurosci* 2007, **27**:942-950.
50. Ruiz A, Campanac E, Scott RS, Rusakov DA, Kullmann DM: **Presynaptic GABAA receptors enhance transmission and LTP induction at hippocampal mossy fiber synapses.** *Nat Neurosci* 2010, **13**:431-438.
51. Xia Y, Zhao Y, Yang M, Zeng S, Shu Y: **Regulation of action potential waveforms by axonal GABAA receptors in cortical pyramidal neurons.** *PLoS One* 2014, **9**:e100968.
52. Chida K, Kaneko K, Fujii S, Yamazaki Y: **Activity-dependent modulation of the axonal conduction of action potentials along rat hippocampal mossy fibers.** *Eur J Neurosci* 2015, **41**:45-54.
53. Chereau R, Saraceno GE, Angibaud J, Cattaert D, Nagerl UV: **Superresolution imaging reveals activity-dependent plasticity of axon morphology linked to changes in action potential conduction velocity.** *Proc Natl Acad Sci U S A* 2017, **114**:1401-1406.
54. Boudkkazi S, Carlier E, Ankri N, Caillard O, Giraud P, Fronzaroli-Molinieres L, Debanne D: **Release-dependent variations in synaptic latency: a putative code for short- and long-term synaptic dynamics.** *Neuron* 2007, **56**:1048-1060.

55. Fields RD: **A new mechanism of nervous system plasticity: activity-dependent myelination.** *Nat Rev Neurosci* 2015, **16**:756-767.
56. Yamazaki Y, Hozumi Y, Kaneko K, Sugihara T, Fujii S, Goto K, Kato H: **Modulatory effects of oligodendrocytes on the conduction velocity of action potentials along axons in the alveus of the rat hippocampal CA1 region.** *Neuron Glia Biol* 2007, **3**:325-334.
57. Wake H, Lee PR, Fields RD: **Control of local protein synthesis and initial events in myelination by action potentials.** *Science* 2011, **333**:1647-1651.
58. Wake H, Ortiz FC, Woo DH, Lee PR, Angulo MC, Fields RD: **Nonsynaptic junctions on myelinating glia promote preferential myelination of electrically active axons.** *Nat Commun* 2015, **6**:7844.
59. Ford MC, Alexandrova O, Cossell L, Stange-Marten A, Sinclair J, Kopp-Scheinflug C, Pecka M, Attwell D, Grothe B: **Tuning of Ranvier node and internode properties in myelinated axons to adjust action potential timing.** *Nat Commun* 2015, **6**:8073.
60. McNaughton BL, Shen J, Rao G, Foster TC, Barnes CA: **Persistent increase of hippocampal presynaptic axon excitability after repetitive electrical stimulation: dependence on N-methyl-D-aspartate receptor activity, nitric-oxide synthase, and temperature.** *Proc Natl Acad Sci U S A* 1994, **91**:4830-4834.
61. Sheffield ME, Best TK, Mensh BD, Kath WL, Spruston N: **Slow integration leads to persistent action potential firing in distal axons of coupled interneurons.** *Nat Neurosci* 2011, **14**:200-207.
62. Hoppa MB, Gouzer G, Armbruster M, Ryan TA: **Control and plasticity of the presynaptic action potential waveform at small CNS nerve terminals.** *Neuron* 2014, **84**:778-789.
63. Novak P, Gorelik J, Vivekananda U, Shevchuk AI, Ermolyuk YS, Bailey RJ, Bushby AJ, Moss GW, Rusakov DA, Klennerman D, et al.: **Nanoscale-targeted patch-clamp recordings of functional presynaptic ion channels.** *Neuron* 2013, **79**:1067-1077.
64. Kawaguchi SY, Sakaba T: **Control of inhibitory synaptic outputs by low excitability of axon terminals revealed by direct recording.** *Neuron* 2015, **85**:1273-1288.
65. Grubb MS, Burrone J: **Activity-dependent relocation of the axon initial segment fine-tunes neuronal excitability.** *Nature* 2010, **465**:1070-1074.
66. Kuba H, Oichi Y, Ohmori H: **Presynaptic activity regulates Na(+) channel distribution at the axon initial segment.** *Nature* 2010, **465**:1075-1078.
67. Kuba H, Yamada R, Ishiguro G, Adachi R: **Redistribution of Kv1 and Kv7 enhances neuronal excitability during structural axon initial segment plasticity.** *Nat Commun* 2015, **6**:8815.
68. Evans MD, Dumitrescu AS, Kruijssen DLH, Taylor SE, Grubb MS: **Rapid Modulation of Axon Initial Segment Length Influences Repetitive Spike Firing.** *Cell Rep* 2015, **13**:1233-1245.
69. Lezmy J, Lipinsky M, Khrapunsky Y, Patrich E, Shalom L, Peretz A, Fleidervish IA, Attali B: **M-current inhibition rapidly induces a unique CK2-dependent plasticity of the axon initial segment.** *Proc Natl Acad Sci U S A* 2017, **114**:E10234-E10243.
70. Desai NS, Rutherford LC, Turrigiano GG: **Plasticity in the intrinsic excitability of cortical pyramidal neurons.** *Nat Neurosci* 1999, **2**:515-520.
71. Cudmore RH, Fronzaroli-Molinieres L, Giraud P, Debanne D: **Spike-time precision and network synchrony are controlled by the homeostatic regulation of the D-type potassium current.** *J Neurosci* 2010, **30**:12885-12895.
72. Kirchheim F, Tinnes S, Haas CA, Stegen M, Wolfart J: **Regulation of action potential delays via voltage-gated potassium Kv1.1 channels in dentate granule cells during hippocampal epilepsy.** *Front Cell Neurosci* 2013, **7**:248.

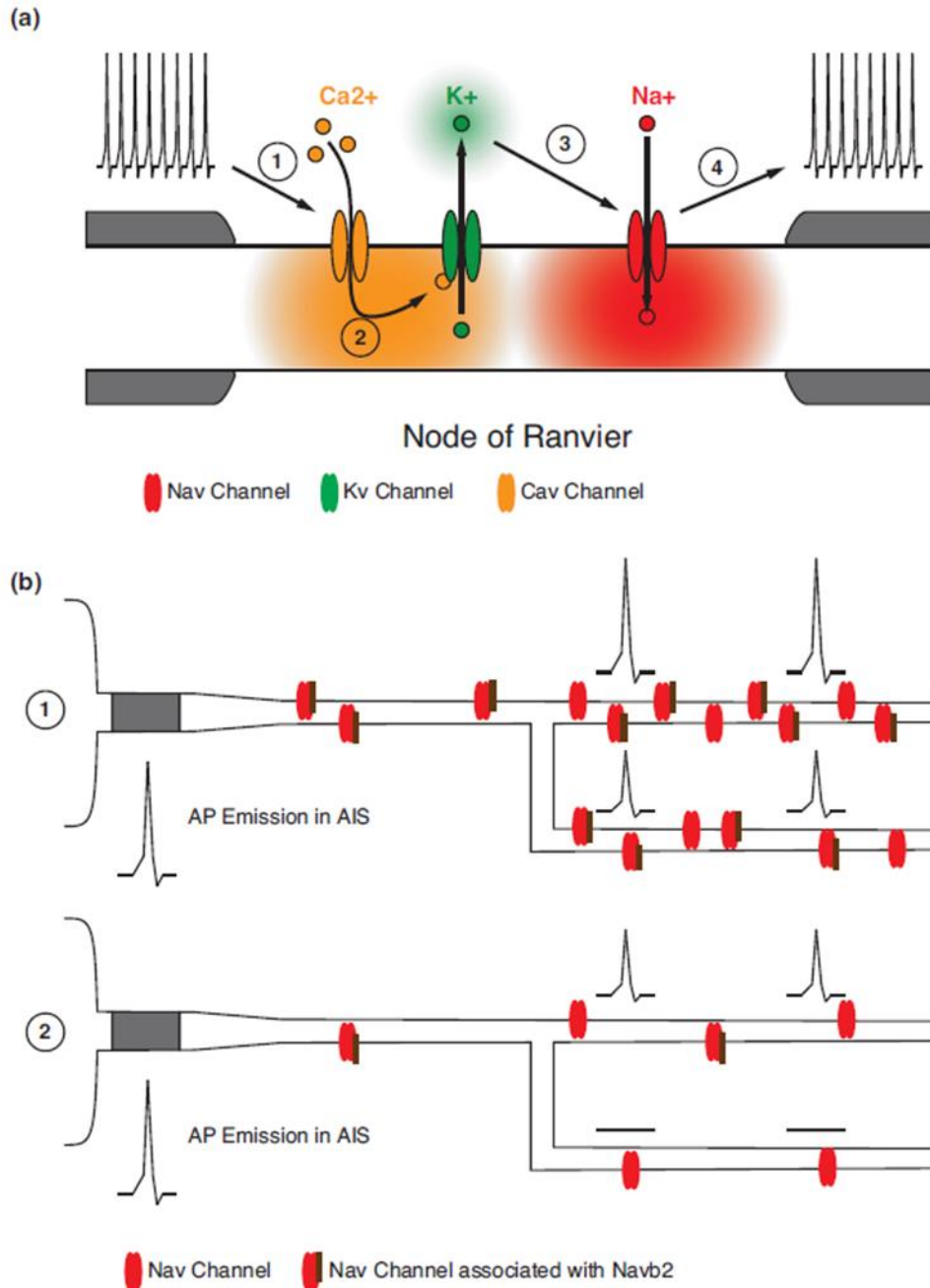


Figure 1. New mechanisms ensuring spikes propagation along the axon. (a) KCa3.1 channels activation avoids conduction failures in Purkinje cells nodes of Ranvier. (1) High frequency spike trains activate low threshold Ca^{2+} current (I_t). (2) Rise of intracellular Ca^{2+} concentration activates calciumdependent 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].

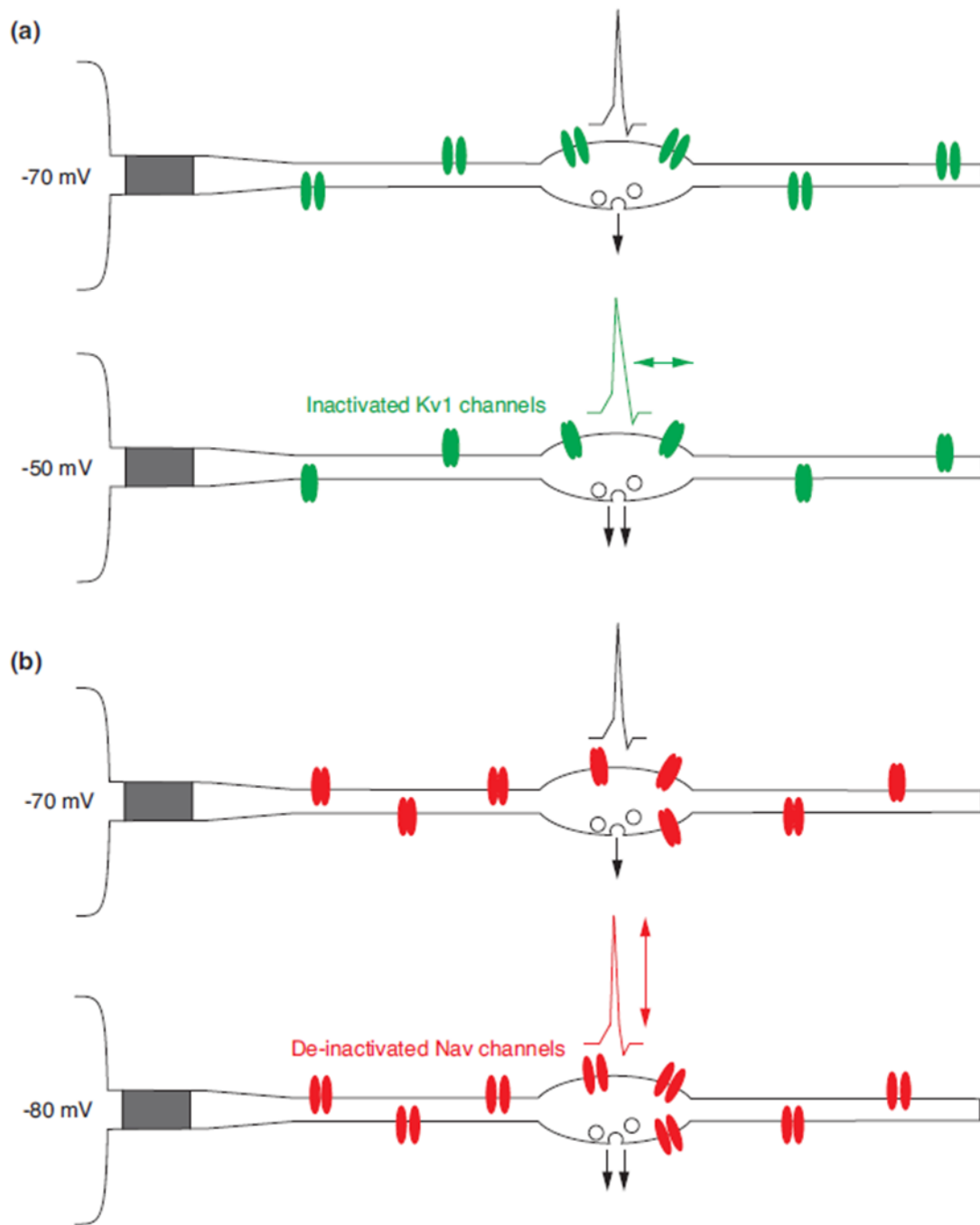


Figure 2. Axonal sodium and potassium channels modulate spike shape and release probability. (a) Top, at resting potential, Kv1 channels are available and insure a quick recovery of depolarization during AP conduction. The resulting AP is thin, producing a moderate calcium entry in the presynaptic bouton 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].

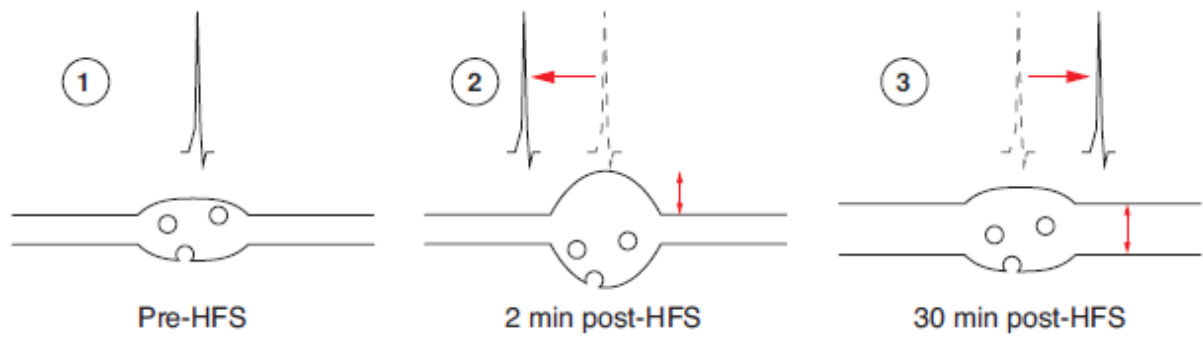


Figure 3. Long-lasting regulation of action potential conduction delay. Left, action potential timing before the high frequency stimulation of the axon. Middle, delayed spike conduction caused by the short-term enlargement of synaptic boutons. Right, long-lasting increase in conduction velocity caused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