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Review article

# The axon as a unique computational unit in neurons

Takuya Sasaki*

*Division of Cerebral Structure, National Institute for Physiological Sciences, Okazaki 444-8787, Japan*

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ABSTRACT

In the mammalian cortex, axons are highly ramified and link an enormous number of neurons over large distances. The conventional view assumes that action potentials (APs) are initiated at the axon initial segment in an all-or-none fashion and are then self-propagated orthodromically along axon collaterals without distortion of the AP waveform. By contrast, recent experimental results suggest that the axonal AP waveform can be modified depending on the activation states of the ion channels and receptors on axonal cell membranes. This AP modulation can regulate neurotransmission to postsynaptic neurons. In addition, the latest studies have provided evidence that cortical axons can integrate somatic burst firings and promote activity-dependent ectopic AP generation, which may underlie the oscillogenesis of fast rhythmic network activity. These seminal observations indicate that axons can perform diverse functional operations that extend beyond the prevailing model of axon physiology.



**Contents**



## 1. Introduction

At the cellular level, the neuronal signaling chain can be divided into several functional components: the dendritic integration of synaptic inputs, AP generation, AP propagation, and synaptic transmission. In the context of information flow, it has been assumed that AP initiation and propagation are regenerative events that never vary in intensity or duration. From this perspective, axons have been regarded as simple cables that faithfully transmit electrical impulses. With the development of direct patch-clamp techniques for small axonal structures, the results of recent neurophysiological studies have begun to challenge this traditional model (Debanne, 2004; Bucher and Goaillard, 2011). Because the generation and propagation of APs are insured by the balance of $Na^+$ influx and $K^+$ efflux through voltage-gated ion channels in axons (Hodgkin and Huxley, 1952), the axonal AP waveform can be modulated by the activation state of these channels and by spatial patterns of axonal arborization (Alle and Geiger, 2006; Shu et al., 2006, 2007; Kole et al., 2007; Sasaki et al., 2011, 2012a). Local shaping of the axonal AP waveform subsequently controls the $Ca^{2+}$ signals at presynaptic terminals and potentiates neurotransmitter release to postsynaptic cells. The most recent studies have demonstrated that APs can be ectopically initiated even from the distal axonal region, which is far from the axon initial segment, by integrating repetitive firings at the soma (Sheffield et al., 2011; Dugladze et al., 2012). These results suggest that axonal fibers can transmit not only digital-like (all-or-none) but also analog-like signals, enabling axons to serve as a unique computational unit to

*Abbreviations:* AP, action potential; eAP, ectopic action potential; AMPA, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid.

* Tel.: +81 564 59 5279; fax: +81 564 69 5276.
*E-mail address:* t.sasaki.0224@gmail.com

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maintain and process a variety of gradient information in neural circuits (Alle and Geiger, 2008). Given that a cortical pyramidal cell locally projects to several hundred postsynaptic targets (Ishizuka et al., 1990; Li et al., 1994; Major et al., 1994), these unique properties of axons may have a significant impact on network dynamics. In this article, I review the recent advances in the understanding of axonal physiology, focusing primarily on hippocampal and neocortical neurons.

## 2. Techniques for direct recording from axons

Traditionally, direct electrophysiological recording from thin axonal fibers has been considered almost impossible due to the relative complexity and small diameters of these structures. Several pioneering studies, however, have overcome this technical issue. In 1994, pioneering works have first demonstrated whole-cell patch-clamp recording techniques from subcellular compartments including dendrites and axons (up to 30 μm from the axon hillock) in cortical pyramidal cells (Stuart and Sakmann, 1994) and cerebellar Purkinje cells (Stuart and Hausser, 1994). Owing to the development of these techniques, axonal initiation and propagation of APs could be clearly demonstrated in various brain regions such as substantia nigra (Hausser et al., 1995). While dendritic recordings have subsequently been utilized to study integration and computation within dendrites, few studies have performed axonal recordings (Colbert and Johnston, 1996; Schmitz et al., 2001), presumably due to technical limitations. For this reason, axonal recordings have been limited to giant axonal structures (3–5 μm), such as the mossy fiber boutons of dentate gyrus granule cells (Fig. 1A; Geiger and Jonas, 2000; Bischofberger et al., 2006)

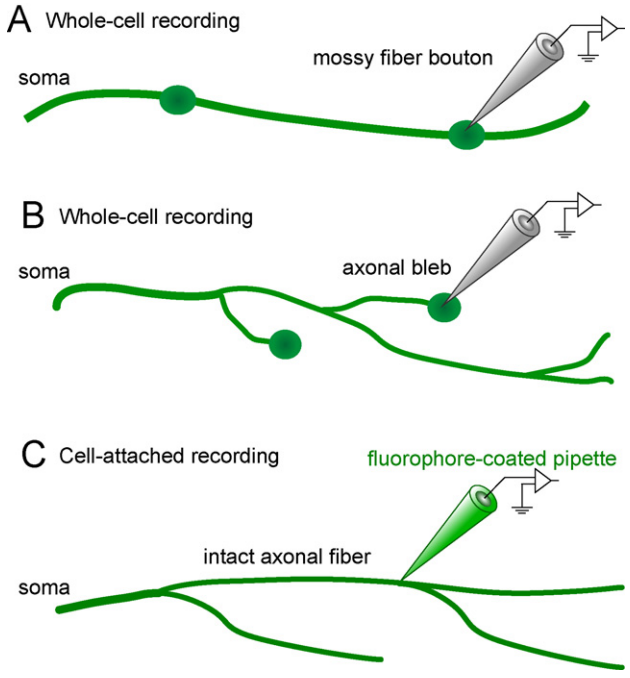


**Fig. 1.** Patch-clamp techniques for recording electrical signals from axons. (A) Whole-cell recording from a mossy fiber bouton of a dentate gyrus granule cell. Presynaptic boutons are directly accessible to the patch electrode due to their large diameters (3–5 μm). (B) Whole-cell recording from an axonal bleb of a cortical pyramidal neuron. Axonal blebs are enlarged structures that form at the cut ends of axons after slicing and (C) Cell-attached recording from an intact unmyelinated axon (~1 μm) of a cortical pyramidal cell. The patch pipettes are coated with a fluorophore, which allows visual targeting of the fluorescently labeled axon using online confocal manipulation. Although this method is only applicable to cell-attached recordings of extracellular AP waveforms, it is relatively easy to perform in comparison with the above two techniques.

and the giant synaptic expansions of the Calyx of Held (Forsythe, 1994; Awatramani et al., 2005). In 2006, Shu et al. reported a technological breakthrough in recording signals from axonal blebs up to 400 μm from the axon hillock in cortical pyramidal cells. After most of pyramidal cell axons are cut during slicing procedure, they form patchable swellings (3–6 μm blebs) at the ends of the axons on the surface of slices (Fig. 1B). The axonal bleb recording technique has been subsequently utilized to study axon physiology in cortical pyramidal cells (Shu et al., 2006; Kole et al., 2007; Sasaki et al., 2011). Recently, we have developed a new patch-clamp technique for the analysis of intact unmyelinated axons (~1 μm) that uses a glass pipette coated with Alexa Fluor-conjugated albumin (Fig. 1C) (Ishikawa et al., 2010; Sasaki et al., 2012c). The advantage of this technique is that fluorescently labeled axon tracts and patch-clamp pipettes can be simultaneously identified in a single fluorescent image without switching back and forth between fluorescence and transmitted images. Although this simplified technique is restricted to cell-attached recordings, similar to previous studies (Clark et al., 2005; Monsivais et al., 2005; Perkins, 2006; Atherton et al., 2008; Palmer et al., 2010; Rudolph et al., 2011; Dugladze et al., 2012), it can be used to measure APs as extracellular unit-like waveforms, which are sufficient to estimate the precise location of AP initiation site (Clark et al., 2005; Khaliq and Raman, 2006; Palmer et al., 2010) or relative changes in the duration of intracellular APs (Sasaki et al., 2012a). These technical advancements in axonal recording techniques will facilitate the further exploration of the density, properties, and distribution of receptors and ion channels on axons.

## 3. Analog modulation of axonal action potential by somatic depolarization

At the resting potential, the duration of somatic APs is constant (Fig. 2A) (Sasaki et al., 2012b), consistent with the general view of AP physiology. However, a different scenario is observed when the soma is sufficiently depolarized. Because neurons contain a variety of voltage-gated $Na^+$ and $K^+$ channels that are required for AP generation, the activation and/or inactivation of these channels can shape AP waveforms. This effect can be easily confirmed by a simple experiment with a somatic whole-cell recording. Subthreshold depolarization just prior to AP initiation at the soma significantly prolongs the subsequent AP waveform (Fig. 2B). The magnitude of the increase in AP duration depends on the depolarization level prior to the AP. The major mechanism underlying the AP broadening is the inactivation of Kv1 channels rather than changes in $Na^+$-channel opening (Shu et al., 2007). It has been estimated that a 10 mV depolarization relative to the resting membrane potential would be expected to inactivate ~10% of the Kv1 channels (Kole et al., 2007). Simultaneous axonal and somatic patch-clamp recordings have revealed that subthreshold voltage fluctuations at the somatodendritic axis propagate a significant distance along the axon in granule cells in the dentate gyrus (Alle and Geiger, 2006) and in pyramidal cells in the prefrontal cortex (Shu et al., 2006). The depolarization propagated along axons can induce AP broadening at axonal regions as well as in the soma, enabling the propagation of broadened APs along axonal fibers. Because the range of the somatic influence is spatially limited by the axonal path length, with a length constant (λ) ranging from 400 to 600 μm (Alle and Geiger, 2006; Shu et al., 2006; Kole et al., 2007), depolarization-broadened APs return to a normal width at some distance from soma (Fig. 2C). In addition to the distance restriction, we recently demonstrated that the AP broadening effect decays more steeply at branch points than at axonal shaft segments (Fig. 2D) (Sasaki et al., 2012a), indicating that branch points act as a filter to modulate the strength of the propagated impulses. This idea is supported by

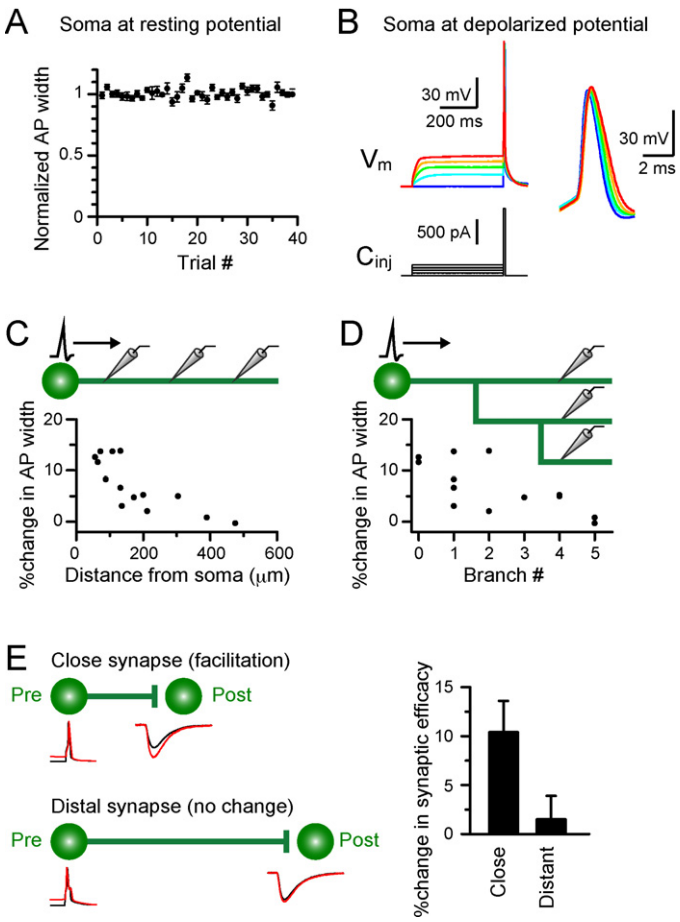


**Fig. 2.** Axonal topology interacts with the somatic modulation of axonal AP broadening and synaptic outputs. (A) The duration of somatic APs initiated from the resting potential is constant from trial to trial. APs were evoked by a somatic current injection every 10 s. (B) Somatic AP width is modulated by depolarization prior to AP initiation at the soma. Voltage traces are color-coded by the amplitudes of the rectangular currents preceding the AP generation. (C and D) Changes in depolarization-induced axonal AP width plotted against the distance from the soma (C) and against the number of branch points (D) that APs traverse. Each curve represents the best fit of the exponential decay function. (E) The somatic depolarization of presynaptic neurons facilitates neurotransmission to close (within 100 μm, top) but not to distant (more than 300 μm, bottom) postsynaptic cells. The traces represent presynaptic APs (left) and postsynaptic currents (right) when the presynaptic CA3 neuron is at the resting (black) or 20 mV depolarized (red) potential and (F) Summary of somatic depolarization-induced changes in synaptic efficacy between close and distant synaptically coupled neurons.

morphological evidence that sibling axon branches are narrower than parent axons and by the cable theory, which defines λ as proportional to the square root of the fiber diameter (Dayan and Abbott, 2001).

One consequence of activity-dependent axonal AP broadening is an intra-axonal elevation of the $Ca^{2+}$ concentration, which favors glutamate release at presynaptic boutons. Optical imaging has confirmed that somatic depolarization prior to AP initiation produces larger AP-induced $Ca^{2+}$ transients in presynaptic boutons than those evoked at the resting potential, which has been demonstrated in hippocampal pyramidal cells (Sasaki et al., 2012a,b) and cerebellar interneurons (Christie and Jahr, 2008; Christie et al., 2011), but not at hippocampal mossy fiber synapses (Alle and Geiger, 2006; Scott et al., 2008). Two potential mechanisms underlying the AP-induced $Ca^{2+}$ dynamics can be proposed: (i) subthreshold depolarization spreads into axon arbor and facilitates $Ca^{2+}$ influx at presynaptic terminals through opening of voltage-dependent calcium channels, albeit at low probability, which is accumulated on the subsequent AP-induced $Ca^{2+}$ influx (Christie et al., 2011), and (ii) broadened APs enhance $Ca^{2+}$ signaling at synaptic terminals by increasing the duration of depolarization. The AP-induced $Ca^{2+}$ increase then facilitates neurotransmitter release from presynaptic terminals. As observed for the depolarization-induced AP broadening effect (Fig. 2C), the depolarization-induced synaptic facilitation also depends on the distance from the soma; somatic depolarization in presynaptic cells strengthens synaptic transmission to close postsynaptic cells but not to distant cells (Fig. 2E). These findings suggest that nearby cortical neurons can communicate with each other in a mixed digital- and analog-like manner through AP conduction along axons.

## 4. The modulation of action potential propagation during axonal conduction

The AP waveform can be transiently modulated even at the middle of an axon while the AP travels down the axon. Debanne et al. (1997), for instance, reported that failure of AP propagation can be induced as a result of the activation of A-type $K^+$ channels on axonal membranes when neurons are briefly hyperpolarized prior to the AP generation. In cerebellar Purkinje cells, simple spikes and spikelets of complex spikes fail to propagate at somatic firing rates of ~200 Hz (Khaliq and Raman, 2005). In a majority of cortical pyramidal neurons, excitatory synapses are formed at focal swellings (axonal varicosities) with intervals of 4–6 μm in an *en passant* manner; these swellings are separated from other varicosities by short axonal shaft segments (Shepherd et al., 2002). It has been reported that presynaptic membranes and axonal shafts express a wide variety of receptors and voltage-dependent ion channels (Engelman and MacDermott, 2004). We recently demonstrated that AP waveforms can also be broadened during axonal conduction (Sasaki et al., 2011). The local application of glutamate to the axonal shaft evokes a broadening of the axonal APs recorded at a point downstream from the drug application site (Fig. 3A). This effect can be mimicked by a local puff of high (20 mM) $K^+$ and 4-aminopyridine (4-AP), an A-type $K^+$ channel blocker. Taken together, these experiments demonstrate that local depolarization at an axonal segment results in AP broadening originating from the focal site through the transient inactivation of $I_A$ conductances (Fig. 3B). The broadened APs elicit larger $Ca^{2+}$ increases in presynaptic boutons and thereby facilitate synaptic transmission to postsynaptic neurons.

In pyramidal cells, most axonal shafts and presynaptic varicosities are in close contact with astrocytes, the largest class of glial cells in the brain. We found that the activation of these periaxonal astrocytes by $Ca^{2+}$ uncaging triggers axonal AP broadening that is dependent on the activation of AMPA receptors (Fig. 3A). This observation suggests that one of the physiological factors that evokes AP broadening might be an extrinsic signal arising from astrocytes, as outlined in Fig. 3B. Similar to the signaling pathway associated with somatic depolarization-induced AP broadening (Fig. 2), the broadened APs facilitate neurotransmitter release at downstream synapses. Another functional implication from this finding is that astrocyte-mediated signaling can influence synaptic outputs at distal regions, well beyond the physical territory of astrocytes (which have a diameter of approximately 50 μm), through the regulation of axon propagation.

Several questions related to this signaling flow remain to be resolved. The most crucial issue is how AMPA receptor activation leads to axonal AP broadening. In cortical pyramidal neurons, it has been debated whether AMPA receptors are expressed on axonal cell membranes (Martin et al., 1993, 1998; Engelman and MacDermott, 2004; Schicker et al., 2008). Two possible pathways could account for local AP broadening: (1) the direct activation of AMPA receptors expressed on axonal membranes could evoke depolarization

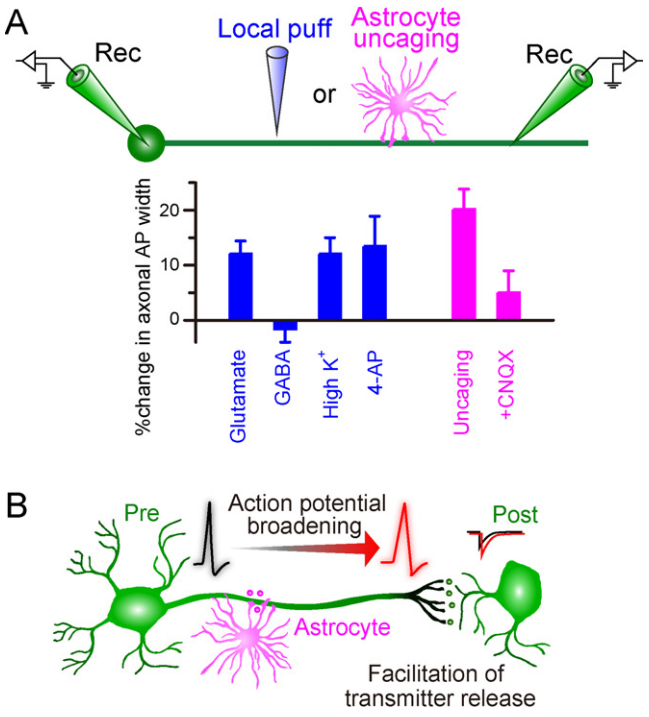


**Fig. 3.** APs are subject to waveform modulation as they travel down axons. (A) Dual somatic and axonal patch-clamp recordings obtained from a hippocampal pyramidal cell. The top panel shows a schematic representation of the recording configuration. Drug application or $Ca^{2+}$ uncaging of astrocytes on the axon path results in a substantial increase in the duration of the APs that are propagated down the axon and (B) A schematic illustration showing how astrocytes regulate neurotransmission at distant synapses through axonal modulation. Local axonal depolarization elicited by periaxonal astrocytes induces AP broadening along axons, which enhances postsynaptic currents. Thus, astrocytes serve as extrinsic instructors of neurotransmission by shaping axonal AP waveforms.

at the axonal segment; or (2) extracellular glutamate could activate AMPA receptors on nearby dendrites, which would in turn increase the extracellular concentration of $K^+$ to indirectly evoke axonal AP broadening. The discrimination of these two mechanisms will require further investigation. Furthermore, glutamate release from astrocytes as a gliotransmitter under physiological conditions is still a matter of debate. Several recent reports have disputed the physiological relevance of gliotransmission (Fiacco et al., 2007, 2009; Agulhon et al., 2008, 2010; Petravicz et al., 2008; Hamilton and Attwell, 2010). However, the $Ca^{2+}$ uncaging method used in our study might be too artificial and nonspecific to truly represent spontaneously generated astrocyte activity. This point also requires future experimental evaluation to better interpret the significance of the astrocyte-axon interaction.

## 5. AP initiation at distal axons independent from the soma

In general, APs propagate orthodromically from the axon initial segment toward axon terminals. Although unidirectional propagation is ensured by the absolute refractory period, the nature of the axons allows APs to propagate equally in both directions. This phenomenon can be observed in a simple electrophysiological experiment. The stimulation of distal axonal fibers triggers ectopic APs, also termed as antidromic APs, originating from the local site, which subsequently conduct toward both the somatodendritic compartment (antidromic direction) and the axon terminal (orthodromic direction). These peculiar APs are distinguishable at the soma by their stereotypical kinetics; the voltage trajectory of ectopic APs increases sharply from the resting potential in the absence of depolarization prior to the AP. The existence of ectopic APs was initially confirmed under pathological circumstances (Pinault, 1995), but more recently, several studies have demonstrated that ectopic APs can occur during active states even in normal cortical networks (Papatheodoropoulos, 2008; Bahner et al., 2011; Sheffield et al., 2011). In a subset of hippocampal and neocortical interneurons, repetitive spikes at the soma are integrated at the distal axonal region and eventually trigger persistent autonomous firing originating from the axonal segment (Sheffield et al., 2011). One of the mechanisms involved in ectopic APs seems to be the opening of gap junctions, rather than somatic depolarization or synaptic transmission, but this point is still unresolved due to the poor specificity of gap junction blockers (Rouach et al., 2003; Chepkova et al., 2008; Tovar et al., 2009; Ye et al., 2009; Behrens et al., 2011). The axonal APs occasionally fail to invade the soma, instead giving rise to prepotentials, termed spikelets, at the somatodendritic compartment (Sheffield et al., 2011). A recent study by Dugladze et al. (2012) provided an important clue about the control of the antidromic propagation of ectopic APs. During *in vitro* gamma oscillation (30–80 Hz) evoked by kainic acid application, ectopic APs are initiated in the distal part of the axon in hippocampal pyramidal cells. Curiously, the somatic invasion by antidromic APs is blocked by the activation of a nearby axo-axonic cell, a type of interneuron that exerts a powerful inhibitory effect on the axon initial segment. These results demonstrate that the axon initial segment has a gating property that determines whether ectopic APs can reach the somatic region and that axo-axonic cells can separate axons from somatodendritic activity during fast network oscillations.

## 6. Possible roles of ectopic APs at distal axons

Although the fundamental significance of ectopic APs has not been fully elucidated, their functional implications are profound. Given that an ectopic AP occurs at the middle of an axonal segment, this type of AP can trigger synaptic transmission to all of the upstream and downstream postsynaptic targets. Therefore, the impact of an ectopic AP might be almost equivalent to that of a somatic AP. Because the frequency of ectopic APs at axons is considerably higher than that of somatic APs during fast network activity (Bahner et al., 2011; Dugladze et al., 2012), the vast majority of ectopic APs may provide a powerful means of information transfer from the hippocampus to other brain regions, such as the neocortex. Another remarkable implication is that ectopic APs are likely to be associated with fast network oscillations such as gamma oscillations and ultrafast ripple oscillations (80–200 Hz), which have been thought to be crucial in memory consolidation (Girardeau et al., 2009; Ego-Stengel and Wilson, 2010) and in transfer from the hippocampus to the neocortex (Buzsaki, 1989; Buzsaki et al., 1992; Eichenbaum, 2000; Diekelmann and Born, 2010; Carr et al., 2011). Previous studies have demonstrated that such fast rhythmic activity is abolished by gap junction blockers, demonstrating that gap junction-mediated electrical couplings are essential for fast network oscillations (Draguhn et al., 1998; LeBeau et al., 2003). Notably, *in vivo* whole-cell recordings from hippocampal pyramidal cells recently revealed that bursts of spikelets and a barrage of postsynaptic currents frequently occur in awake animals (Harvey et al., 2009; Maier et al., 2011; Chorev and Brecht, 2012), and both of these phenomena are well phase-locked to the high-frequency oscillation in local field recordings. In combination with the fact that somatic spikelets represent ectopic APs initiated at axonal compartments through electrical coupling, as mentioned above (Bahner et al., 2011; Sheffield et al., 2011; Dugladze et al., 2012), it might be possible that ectopic APs are involved in the initiation and/or maintenance of fast network activity. Consistent with this idea, anatomical and electrophysiological evidence has implied

the presence of gap junctions between axons at a site 50–120 μm from the soma (Gladwell and Jefferys, 2001; Schmitz et al., 2001). However, the density of axonal gap junctions seems extremely low (approximately 1–2 per neuron) (Traub et al., 1999), and understanding the exact nature of this phenomenon will require further evaluation. In line with this hypothesis, an *in vitro* study using hippocampal slices has shown that high-frequency oscillations can be generated even when the axonal plexus in the striatum oriens is isolated from the pyramidal cell bodies (Traub et al., 2003a). Correspondingly, *in silico* network models also predict that the electrical coupling of pyramidal cell axons contributes to the formation of high-frequency oscillations (Traub et al., 1999, 2003b, 2012; Traub and Bibbig, 2000; Bahner et al., 2011). These observations are plausible in terms of the kinetics of intercellular interactions because general chemical synapses alone might be too slow to account for such high-frequency (80–200 Hz) oscillations. Thus, electrical couplings might be more effective mechanisms for synchronizing the activity in a bundle of axons at such a fine temporal scale. Through these unique intercellular communications, ectopic axonal APs might play a central role in the generation and maintenance of cortical oscillations, independent of somatodendritic activity.

## 7. Concluding remarks and future perspectives

Thanks to the recent achievement of direct axonal recording in the mammalian cortex, a growing number of studies have revealed fascinating roles for axons that challenge the conventional all-or-none view of APs. In combination with non-linear somatodendritic integration, axonal computation may contribute to enriching the information processing capabilities of single neurons. This paper introduced two unique properties of cortical axons; modulation of AP waveform and ectopic AP initiation. Although it has been still unknown whether these properties are linked with each other, it is possible to consider their relationships. For example, ectopic APs initiated in the axon that propagate orthodromic and antidromic directions could be differentially affected by somatic depolarization due to the location dependency of depolarization-induced broadening of axonal APs. Other possible event is that broadened APs might be more effective to trigger ectopic APs from axonal segments compared with APs induced from resting potential. Future studies are needed to clarify these phenomena. In addition, several details concerning the subcellular mechanisms of these phenomena also remain unresolved; for example, the distribution of ion channel clusters on complex axonal trees, the factors driving signaling pathways that modulate axonal conduction, the physiological conditions required for ectopic AP generation, and the frequency of conduction failures are all unknown (Dyball et al., 1988; Baccus, 1998; Soleng et al., 2003). At the neural circuit level, it remains unknown how many synapses are scaled by transient changes in analog-like AP waveforms and how effectively axonal AP dynamics serve to upgrade neural population coding. Answering these questions will require substantial advances in recording techniques for axons, including quantitative immunofluorescence methods (Kole et al., 2008; Kuba et al., 2010) and optical imaging techniques with higher temporal and spatial resolution using genetically encoded $Ca^{2+}$ indicators (Dreosti et al., 2009; Tian et al., 2009; Zhao et al., 2011; Ohkura et al., 2012), $Na^{+}$ indicators (Kole et al., 2008), and voltage-sensitive dyes (Palmer et al., 2010; Popovic et al., 2011). Optogenetic tools will enable to stimulate local axonal sites and examine how the evoked APs spread throughout axonal branches. In addition, more realistic computational models will also be indispensable to quantitatively predict the potential consequences of single-axonal computation for neural circuit functions with respect to the storage of working memories and information processing capability. Unveiling novel axonal function using these innovative approaches will facilitate our understanding of the limits of single-neuron computation.

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