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Somatic modulation of ectopic action potential initiation in distal axons

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Classically, action potentials are initiated at the axon initial segment (AIS) when the summed depolarizing events arising from the dendrites exceed a threshold value. Then, action potentials propagate along the axon before reaching presynaptic terminals where they cause local calcium influx and transmitter release. According to this scheme, the AIS is a major player since all propagated excitation is precisely initiated at this hot spot endowed with a high concentration of sodium channels. However, sodium action potentials may be generated at regions remote from the AIS, that is, at ectopic sites located in the axon.

Ectopic action potentials (EAPs) can be initiated in distal parts of the axon and travel antidromically along the fibre to invade the soma. Such ectopic spikes have been recorded during fast hippocampal oscillations *in vitro* (Dugladze *et al.* 2012) or during spatial exploration *in vivo* (Epsztein *et al.* 2010), but they also occur in several neuronal pathologies such as epilepsies or demyelinating diseases. The precise way EAPs can be initiated is not yet properly defined but it is thought that local depolarization mediated by spiking activity in adjacent axons through gap junctions (Schmitz *et al.* 2001) or stochastic activation of sodium channels in demyelinated segments of the axon (Hamada & Kole, 2015) might initiate EAPs. Compared to AIS-evoked action potentials that are classically initiated on the top of a slow subthreshold depolarization such as an excitatory postsynaptic potential, EAPs recorded in the cell body display a much lower threshold (~ -20 mV) (Hamada & Kole, 2015). This lower threshold is thought to result from the axial current flow initiated distally in the axon that propagates back to the soma. In this case, the spike is initiated without subthreshold

depolarization generated in the soma, thus avoiding inactivation of sodium channels in the axon. The backpropagation of EAPs is controlled by synaptic inhibition mediated by axo-axonic interneurons that target the AIS (Dugladze *et al.* 2012). As a result, most of EAPs do not propagate to the soma during hippocampal gamma oscillations. While the control of EAP backpropagation has been characterized, it was yet unknown to what extent synaptic potentials arising from the somato-dendritic pole can control their initiation in the axon.

In this issue of *The Journal of Physiology*, Thome and coworkers (2018) have answered this question by showing that spontaneous or evoked synaptic activity generated in the somato-dendritic compartment is transmitted with little attenuation ($\sim 20\%$) and over long distances (> 300 μm) in axons of CA1 pyramidal cells (Thome *et al.*, 2018). Voltage transients were even amplified in the proximal region of the axon. For this, the authors obtained simultaneous whole-cell patch-clamp recordings from the soma and the axon of individual CA1 pyramidal neurons and they compared amplitudes of excitatory postsynaptic potentials (EPSPs) measured in the somatic and axonal compartments. While synaptic responses displayed little attenuation when recorded in the axon, the opposite was not verified since subthreshold potentials generated in the axon were found to be strongly attenuated in the somatic compartment ($\sim 85\%$). Next, Thome *et al.* examined the role of evoked excitatory and inhibitory synaptic potentials in the generation of EAPs. The probability of evoking an EAP by extracellular stimulation of the alveus was greatly enhanced when EPSPs were evoked simultaneously (Thome *et al.*, 2018). In contrast, EAPs were less successful when inhibitory postsynaptic potentials (IPSPs) were evoked with an extracellular stimulating electrode located near the soma. The relative timing between synaptic responses and EAP was found to be critical, suggesting the possible contribution of such a mechanism in fast network oscillations. Thus, the findings of Thome and coworkers strongly suggest that modulation of ectopic excitability depends on propagation of somatic voltage deflections to the axonal site of EAP initiation in a time-dependent manner.

This paper is important because it opens several interesting perspectives. First, the fact that synaptic inputs arising from the somato-dendritic region modulate EAP initiation challenges the view that the distal axon is electrically independent from the soma. In fact, recent estimations of the space constant in axons give values ranging between ~ 200 and ~ 1000 μm , depending on the cell type. The originality of the findings of Thome *et al.* resides in the fact that the space constant in the axon of CA1 pyramidal neurons was found to be highly polarized towards the axonal pole, due to the difference in somatic and axonal capacitance. Second, the facilitation of EAP induction caused by synaptic excitation may prove to be a factor aggravating cellular hyperexcitability and epileptic network discharges under pathological conditions. In addition, the time dependence of ectopic firing modulation by synaptic inputs suggests that this process may contribute to the high precision of action potential timing during fast network oscillations. Most previous studies devoted to the coupling between somatic and axonal compartments have focused on describing the impact of axonal ion channels on firing properties measured in the cell body (Kole, 2011; Rama *et al.* 2017). The original contribution of Thome *et al.*'s findings resides in showing that electrical activity at the input side is detected by the axon over long distances to determine whether an EAP can be triggered or not. In this study, EAPs were evoked by electrical stimulation of distal axons. Future studies will have to identify precisely the trigger and the site of initiation of EAPs in axons. There is no doubt that these questions will be quickly resolved.

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Additional information

Competing interests

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Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.