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Astrocytes Shape Axonal Signaling

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Abstract

Axons perform two major functions that underlie the electrical activity of neurons. They generate action potentials in the axon initial segment and enable propagation of action potentials to the presynaptic terminal to trigger chemical signaling to postsynaptic neurons. The action potential waveform can be modulated by intrinsic factors such as axon geometry or biophysical properties that eventually enhance neurotransmitter release. This view has been extended by new evidence showing that extrinsic signals arising from astrocytes also control the action potential waveform and influence synaptic strength. This plasticity is independent of the tripartite structure formed by astrocytes with the neuronal pre- and postsynaptic elements. By shaping axonal action potential waveform, astrocytes act as extrinsic instructors of glutamatergic transmission in the hippocampus.

Axons are involved in two major operations that determine neuronal output: (i) the initiation of the action potential at the axon initial segment and (ii) the active propagation of action potentials from this proximal region of the axon to the axon terminal (1, 2). Generally, axons are considered to be reliable transmission cables in which stable propagation occurs once an action potential is generated. However, increasing evidence suggests that the axon is also the locus of several operations that determine signal processing in synaptic circuits, neuronal timing, and synaptic efficacy (3). For instance, in response to certain stimuli action potentials fail to propagate (4, 5) or propagate backward (6) at axonal branch points. Repetitive firing leads to axon-specific spike broadening because of inactivation of potassium channels that subsequently enhances presynaptic glutamate release (7). Axons integrate slow synaptic potentials arising from the somatic and dendritic compartments that modulate voltage-gated ion channels in the presynaptic terminal and alter spike-evoked synaptic transmission (Fig. 1, A and B). For instance, slow depolarization below the spike threshold increases synaptic strength (8–12). Thus, axons signal both digital (namely, action potentials) and analog (namely, slow synaptic potentials) events (13) through the inactivation of axonal potassium channels or the modulation of basal calcium concentrations and spike-evoked increases in terminals (14, 15). These mechanisms of regulating axonal processing are intrinsic because they rely on both axon geometry and the biophysical state of axonal ion channels. Sasaki et al. (16) now extend this view by showing that extrinsic signals arising from astrocytes—the largest class of glial cells in the brain—can also transiently modulate the width of action potentials in axons. Using an elegant combination of electrophysiological and confocal imaging techniques, the group of Ikegaya showed that stimulation of peri-axonal astrocytes causes broadening of action potentials in axons of CA3 pyramidal neurons through the activation of AMPA-type glutamate receptors (Fig. 1C). The consequence of spike broadening is an intra-axonal increase in calcium concentration that favors glutamate release at en passant boutons. Thus, local activation of the astrocytic network can modulate axonal properties and, in turn, facilitate synaptic transmission.

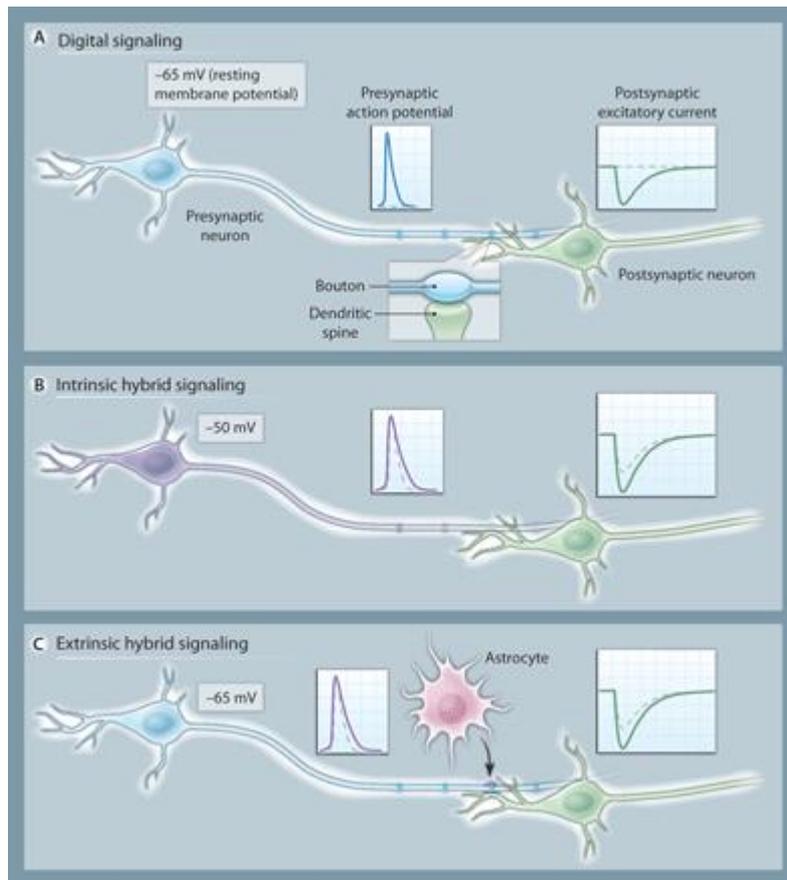


Fig. 1

Multiple modes of cortical axon signaling. (A) Digital signaling. Postsynaptic responses (gray traces) are determined in an all-or-none fashion by the presynaptic action potential generated in the axon initial segment and propagated along the axon. (B) Intrinsic digital-analog (hybrid) signaling. Propagation of subthreshold depolarization (-50 mV) from the somatodendritic compartment to the axon enhances synaptic transmission triggered by action potentials. In this case, the action potential width is extended and thus facilitates neurotransmitter release. (C) Extrinsic digital-analog (hybrid) signaling. Glutamate released by the astrocyte depolarizes the axon locally, increases the width of the action potential, and facilitates synaptic transmission [adapted from (16)].

Other studies have also stressed the importance of astrocytes in fast synaptic transmission. Astrocytes occupy a strategic position in the brain. Because of their highly ramified morphology, they tightly interact with the pre- and postsynaptic neuronal elements to form a tripartite synaptic complex (17, 18). The glutamate transporters on the surface of astrocytes endow these cells with the ability to regulate synaptic transmission by controlling glutamate diffusion and concentration in the extracellular space (19, 20). As a consequence, astrocytic coverage determines short-term plasticity of synaptic transmission through the modulation of presynaptic glutamate receptors (21). There is now strong evidence that slowly occurring (seconds to minutes) elevations in intracellular calcium concentration are triggered in astrocytes after activation of G protein-coupled receptors by synaptically released neurotransmitter. A striking consequence of this astrocytic activity seems to be the capacity of astrocytes to release glutamate and other gliotransmitters, such as adenosine 5'-triphosphate and d-serine, in a soluble N-ethylmaleimide-sensitive factor (NSF) attachment protein (SNAP) receptor (SNARE)-dependent manner (22, 23). In fact, glutamate released from astrocytes

generates slow transient currents in pyramidal neurons that are mediated by the activation of N-methyl-d-aspartate (NMDA) receptors (24). Astrocytes also play the role of cellular relay between pyramidal neurons by mediating depolarization-induced facilitation of synaptic transmission in the CA1 region (25). The release of d-serine from astrocytes has been suggested to facilitate induction of long-term synaptic potentiation by its modulatory action on postsynaptic NMDA receptors (26, 27), although another study has shown that long-term potentiation induction is not modulated by astrocyte Ca²⁺ signaling (28). The data of Sasaki et al. (16) is consistent with the release of glutamate by astrocytes because axonal spike broadening was blocked by an antagonist against glutamate receptors. Beyond their classical modulation of synaptic transmission by the recapture of glutamate or the release of gliotransmitter that affect the pre- or postsynaptic elements, astrocytes are now shown to regulate neuronal communication by directly acting on the axon, upstream to the tripartite structure. Axonal spike broadening was not affected by inhibiting glutamate transporters or by buffering intraneuronal calcium, but was abolished by an AMPA receptor antagonist and mimicked by direct local application of glutamate to the axon. Notably, the amount of synaptic facilitation obtained at CA3-CA3 connections (~12%) is similar to that observed when the axonal spike is enlarged by depolarization of the cell body (11). However, a striking difference between these two modulations is that the astrocyte-dependent modulation of spike width affects only a relatively small portion of the axon, whereas depolarization of the cell body is expected to broaden the spike in many boutons along the axon over a distance defined by the axon space constant (Fig. 1C).

Glia-axon interactions were initially thought to be mainly restricted to the production of the myelin sheath by oligodendrocytes that covers axons and allows faster conduction velocity (29, 30). However, accumulating evidence has revealed interactions between astrocytes and axons. In myelinated axons, perinodal astrocyte processes establish contact with the nodal membrane of the axon to buffer ion concentrations in the extracellular perinodal space (31, 32). The study of Sasaki et al. (16) broadens this view by showing that astrocytes also interact with axons to shape neuronal transmission. However, many questions remain to be addressed. First, a single astrocyte covers a spherical volume with a diameter of ~40 μm (33). Therefore, activity of an astrocyte may affect a large population of axons, creating volumes of enhanced synaptic transmission. The consequences of this regulation on hippocampal network activity must also be explored. Second, astrocytes display spontaneous calcium fluctuations that propagate over the astrocytic network by way of gap junctions (34). Calcium propagation into specific astrocytes or astrocytic processes may influence interneuronal transmission, and the general principles governing the regulation of cell-cell communication within these networks have yet to be discovered. Third, the mechanisms by which the many functions of astrocytes in the central nervous system (neurovascular coupling, control of ionic and metabolism environment in the neuropil, partners of the tripartite synapse, and regulators of axonal spike waveform) are coordinated remain to be clarified. Fourth, astrocytic calcium activity is at least two orders of magnitude slower than that of sodium spikes. This implies that astrocytes are probably implicated in regulatory mechanisms that differ from the fast coincidence-detection processes classically described in the brain. Rather, astrocytes may be implicated in slow neuronal adaptation, such as homeostatic mechanisms or developmental regulation. It can be expected that in the future, a complete picture integrating these previously unknown facets of neuron-glia interactions will emerge.

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