

Determining Excitability of Cortical Neurons and Their Recurrent Network

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Cortical neurons communicate in both digital and analog modes. The digital signal is the all-or-none action potential (AP) initiated first at the axon initial segment (AIS). The ability of generating APs determines the excitability of a given neuron. The analog mode of communication reflects the modulation of synaptic strength by presynaptic membrane potential. The average amplitude of AP-triggered postsynaptic responses increases with presynaptic depolarization. We investigated the underlying mechanism for the two modes of communication, and the role of analog signaling in regulating the balance of excitation and inhibition in the cortical network.

For the generation of digital signals (neuronal excitability), we performed patch-clamp recordings from cortical axons in brain slices, together with immunostaining experiments, and found that different subtypes of voltage-gated sodium channels play distinct roles in mediating AP initiation and propagation. In excitatory pyramidal cells (PCs), subtype Nav1.6 accumulated at the distal AIS mediates AP initiation, whereas Nav1.2 concentrated at the proximal AIS promotes AP backpropagation to the soma and dendrites. In inhibitory interneurons, we found the expression of Nav1.1 and Nav1.6 at the AIS of parvalbumin-containing neurons. In addition to these channel subtypes, we also observed the expression of Nav1.2 at the AIS of somatostatin-positive interneurons. The distinct channel subtype composition could be attributable to the difference in AP threshold in the two cell types. For the role of analog signaling, we performed whole-cell recordings from cortical neurons and found that subthreshold depolarization in presynaptic PC substantially enhances disynaptic inhibition in neighboring cells. By performing recordings from PC and inhibitory interneurons, we revealed that subthreshold depolarization in PC caused facilitation of AP-induced excitatory postsynaptic potentials in interneurons, leading to increased firing probability and AP number, and therefore enhanced inhibition in nearby neurons. Thus, analog signaling has profound effect on the operation of cortical microcircuits that mediates recurrent inhibition. Together, our results provide some insights into the mechanism that determines neuronal excitability and the way of cortical network to maintain the balance of excitation and inhibition.