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FUNCTIONAL ROLE OF AXON HILLOCK AND INITIAL SEGMENT IN CORTICAL SPIKE INITIATION. J.R. Huguenard*#, J. Joerges, Z.F. Mainen and T.J. Sejnowski. Howard Hughes Medical Institute, Salk Inst., La Jolla, CA 92037 and #Dept. of Neurol., Stanford Univ. Sch. Med., Stanford, CA 94305.

The processes that lead from synaptic input to spike output are critical factors in information processing in cortical neurons, yet the precise mechanisms of spike initiation are not well understood. Although neocortical pyramidal cells have voltage-dependent somatic and dendritic Na^+ channels that could promote dendritic spikes, recent data [Stuart and Sakmann, Nature 367:69] support the long-standing hypothesis that spikes are initiated preferentially in the axon hillock or initial segment (AH-IS). This is consistent with our findings in acutely isolated neurons that only cells retaining a visually detectable axon segment can support robust spike generation. A biophysical model was constructed in order to explore the implications of these findings.

When reported somatic and dendritic Na^+ densities (40 pS/μm^2) are combined with AH-IS densities at least 200-fold higher, a density comparable to measurements at nodes of Ranvier, spikes are initiated in the initial segment and then invade the soma and dendritic tree antidromically, even when the site of depolarization is in the distal dendrite. In addition to high channel density, the geometry of the AH-IS was found to be critical to this behavior. The IS achieves a lower initiation threshold by a combination of high local current density and electrical isolation from the soma, while the conical shape of the AH promotes complete invasion of spikes into the soma. Simulations of axo-axonic inhibition, as believed to occur at chandelier cell synapses on the AH-IS, demonstrate that this type of inhibition is more effective in delaying spike onset than equivalent inhibition in the somatodendritic compartment. Voltage-clamp simulations indicate that caution should be exercised in the interpretation of somatic voltage-clamp data. For example, IS spike initiation can occur after distal dendritic synaptic input, even with apparent voltage clamp in the soma. These results underscore the capacity of the AH/IS to function independently of the soma, and indicate the importance of further studies of its physiology. Supported by NIH Grant NS12151 and Office of Naval Research. ZFM is an HHMI Predoctoral Fellow.