On the upper threshold phenomenon of extracellular neural stimulation

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TO THE EDITOR: Although the authors reported interesting findings (Boinagrov et al. 2012), well-known facts such as “the axon is the most excitable part of a neuron” (Nowak and Buhl 1998) or “axonal sodium-channel bands shape the response to electric stimulation in retinal ganglion cells” (Fried et al. 2009) cannot be shown using their presented simple spherical neuron model. Therefore, I reanalyzed the upper threshold phenomenon with a compartment model of a retinal ganglion cell (RGC) (Rattay 1999, 2013; Rattay et al. 2003; Rattay and Resatz 2004; Werginz et al. 2014). Instead of full 3D evaluations, models for extracellular neural stimulation are often reduced to an electrical network for the currents along the axes of neurites (longitudinal mode, cable equation) or in transverse direction (Boinagrov et al. 2012; Meffin et al. 2012). Here, the soma was segmented into three compartments orthogonal to the retina (transverse direction) to study the reversal of the sodium ion current at strong depolarizations. The axon and the dendrite were simulated in the longitudinal mode.

The RGC model of Fig. 2 in Jeng et al. (2011) was simplified (Fig. 1) and stimulated with a point source and a virtual electrode of inverted polarity to simulate a ground electrode representing a situation as in Fig. 2 of Boinagrov et al. (2012). The FCM model (Fohlmeister et al. 1990) was used for the soma as in Jeng et al. (2011), and its sodium and potassium currents for the axon with 5-fold ion channel densities within the sodium band and 0.2-fold ion channel densities in the dendrites. Intracellular resistivity was 0.3 kΩ·cm, retina resistivity 5.05 kΩ·cm.

Applying 0.2-ms cathodic pulses showed similar responses of the compartment model in the soma as reported in Fig. 2 of Boinagrov et al. (2012): Spikes were elicited for cathodic stimuli between −0.97 μA and −10 μA. The −10.8-μA pulse response was blocked as a consequence of the strong hyperpolarization of the soma (Fig. 1, left traces). However, in contrast to the spherical model approach, the sodium current influx within the sodium band caused a propagating spike along the axon for the −10.8-μA pulse (right traces). The result for this configuration is a one-sided firing for strong cathodic stimuli.

All simulated spikes shown in Fig. 1 were initiated within the sodium channel band. As spike elicitation is short for strong pulses, the latencies at the axon (right traces) decreased for increasing stimulus intensity. Enlarging pulse amplitude resulted in stronger hyperpolarization at the soma region that delayed spike conduction from the sodium band towards the soma. Consequently, the −2-μA spike appears later than the −0.98-μA spike in the left traces of Fig. 1. Reducing the pulse a bit below −0.98 μA (not shown) resulted again in a larger somatic spike initiation delay that is not much disturbed by the weak hyperpolarization. The consequence is a U-shaped latency-intensity relationship with a rapid increase near the lower and upper thresholds as recorded at the somas of retina cells (Fig. 3 of Boinagrov et al. 2012).

As demonstrated by Boinagrov et al. (2012), reduction of the extracellular sodium ion concentration decreases the Nernst potential, e.g., of 20 mV, which caused a shift of the somatic block phenomenon limit from −10.8 μA to a lower value (−8 μA), smaller (axonal) spike amplitudes (Fig. 1, bottom), and a higher electrode threshold current of −1.06 μA. Note the high amplitude of the transmembrane voltage in the sodium band, which initiates possible spikes in the sodium channel band and not at the soma. The compartment model analysis demonstrates that the cathodic soma block phenomenon depends essentially on the electrode position relative to the axon. Curvature of the axonal pathway (Eickenscheidt and Zeck 2014; Schiefer and Grill 2006) and the electrode position relative to the region with high sodium channel densities (Fried et al. 2009; Jeng et al. 2011)
are sensitive key parameters with high impact on the occurrence of the block phenomenon and the lower and upper threshold values. When the $x$-coordinate of the electrode is a bit reduced, the strong somatic hyperpolarization decreases (simulated but not shown) and the blockage phenomenon vanishes.

Sodium ion current reversal on the depolarized side of the cell membrane as described in Boinagrov et al. (2012) may cause an upper threshold phenomenon at the soma without any axonal spiking for certain conditions. However, in most cases of extracellular stimulation, spikes are expected to be initiated in the axon even for strong pulses. The presented example (Fig. 1) demonstrates that the U-shaped latency-intensity relationship as well as the reduction of external sodium concentration also supports the conventional cathodic block hypothesis (Ranck 1975; Rattay 1987, 1999).

DISCLOSURES

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AUTHOR CONTRIBUTIONS

F.R. conception and design of research; F.R. performed experiments; F.R. analyzed data; F.R. interpreted results of experiments; F.R. prepared figures; F.R. drafted manuscript; F.R. edited and revised manuscript; F.R. approved final version of manuscript.

REFERENCES


