Mechanisms of the Block of Excitation at High-Intensity Extracellular Microelectrode Stimulation - A Model-Based Study

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Abstract

The extracellular stimulation of neurons is a technique to provoke the electrical activity of nerve cells. Understanding the mechanisms behind excitation and inhibition of neural activity by electrical pulses is crucial for the design of neural prostheses, like retinal implants. The stimulation window defines the range of stimulation intensities capable of eliciting an action potential for a particular stimulation setup.

Different blocking phenomena at high-intensity extracellular stimulation are known. An anodal surround block prevents the passing of an action potential due to strong hyperpolarizations, the upper threshold prevents the action potential due to a sodium current reversal. By computational modeling, the blocking phenomena were investigated. In a multi-compartment model, the non-linear system of ordinary differential equations is solved by the implicit backward Euler method. The finite element method uses mathematical variation methods to approximate the overall solution within accepted error margins.

In the simulations, monophasic and biphasic rectangular current-controlled pulses from a microelectrode are applied to spherical cells, retinal ganglion cells, and human myelinated fibers modelled by widely accepted cell membrane models.

The implementation of the active cell membrane in a 3D finite element model is unique in many aspects; especially, the double-cable model for the myelinated fiber has never been implemented before, to the author's best knowledge.

Three key-mechanisms causing the upper threshold were identified by analyzing the spherical cell: (i) strong potassium currents, (ii) inactivated sodium ion channels, and (iii) the already known sodium current reversal. While mechanisms (i) and (ii) always contribute to some extent to the upper threshold, a sodium current reversal is often but not necessarily involved. The upper threshold is characterized as a situation where repolarizing forces outmatch depolarizing forces before an action potential has been elicited.
For retinal ganglion cells stimulated with monophasic pulses, it could be shown that for electrode positions close to the soma, the upper threshold in the soma has a decisive role in blocking the action potential in the axon. Further, also in the retinal ganglion cell, a sodium current reversal is not necessarily present. For biphasic rectangular pulses, the block of actions potentials usually occurred at far higher stimulus amplitudes compared to the monophasic cathodic case. In the asymmetric case (longer but weaker anodic pulse), it could be shown that a pseudo-monophasic 'cathodic first' pulse can have an only slightly higher upper limit than the monophasic case. This pulse form could be used as an active inhibition strategy in neural prostheses.

For myelinated fibers, no relevant contribution of the upper threshold in the action potential block was found. Here, the anodal surround block already blocks the action potential at stimulus amplitudes below the level where strong repolarizing forces are developed.

In conclusion, the mathematical modeling of extracellular stimulation setups showed that the block at high stimulation intensities cannot be traced back to a moncausal explanation. Due to the non-linear temporal aspects of the ion channel kinetics, a complex multi-dimensional system of competing de- and repolarizing forces has to be simulated in order to predict whether an action potential is generated and whether this action potential is conducted along the axon.