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Modeling the GABA and ephaptic feedback mechanisms in cat outer retina

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Background

In cat, the onset of dim backgrounds can enhance small-spot flicker responses of retinal horizontal cells [1]. This is called background-induced flicker enhancement. A biophysical model involving neural subcircuits in the outer-plexiform layer (OPL) of the retina was proposed to explain the enhancement effect [2]. The model states that hyperpolarization of horizontal cell dendritic terminals, conducted centripetally through gap junctions from rod-induced hyperpolarization of peripheral horizontal cells, increases the flow of calcium into the cone synaptic pedicle, stimulating transmitter release by the cone presynaptic apparatus, and resulting in an enhanced postsynaptic cone response. It remains controversial as to what causes the increased calcium entry in response to horizontal cell hyperpolarization, and two hypotheses which are hotly debated have received the most attention. The first hypothesis proposes that hyperpolarization of the horizontal cell reduces the release of a blocking agent (most likely gamma-aminobutyric acid (GABA)) from the horizontal cell, allowing more calcium to enter the cone synaptic terminal [2]. The second hypothesis contends that the rise of calcium current is GABA independent and is caused by an ephaptic mechanism in which hemichannels (half of a gap junction) and a relatively high intersynaptic resistance play the key role [3,4]. It speculates that hyperpolarization of horizontal cells leads to an increased hemichannel-mediated current flow through the intersynaptic cleft into the horizontal cell. As a result, the potential drop over the intersynaptic resistance will increase, and the nearby voltage-dependent calcium channels in the cone membrane will sense a local depolarization, giving rise to an augmented calcium influx. Although several experiments seem to support the ephaptic hypothesis [3,5,6], some recent experimental [7] and computational [8] analyses question its significance. However, it is still premature to dismiss the ephaptic hypothesis based on these recent results.

Computational study

A partial differential equation model for the subcircuits in the retinal OPL that incorporates both the GABA and ephaptic mechanisms is formulated, in which the collection of horizontal cells is treated as a two-dimensional conductive sheet due to the presence of numerous gap junctions between horizontal cells. Simulations are conducted for different test regions and compared to experimental data for the enhancement effect in cat retinal horizontal cells. The results provide insight into which of the competing hypotheses for calcium entry is appropriate, and may suggest the possibility of a hybrid mechanism combining both the GABA and ephaptic hypotheses.

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