A Mathematical Model of Signal Propagation in the Starburst Amacrine Cell Network

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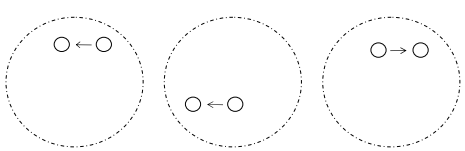
1. Abstract

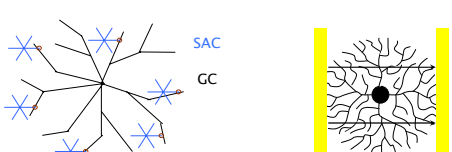
Displaced starburst amacrine cells (SACs) are retinal interneurons that exhibit $GABA_A$- and Cl cotransporter-mediated, directionally selective (DS) light responses in the rabbit retina. They depolarize to stimuli that move centrifugally through the receptive field surround and hyperpolarize to stimuli that move centripetally through the surround (Gavrikov et al., 2003, 2006). We have begun to model the SACs and their associated retinal network to examine the circuitry and mechanisms that underlie their responses to moving and stationary light stimuli.

Previous computational work on direction selectivity (Borg-Graham and Grzywacz, 1992; Tukker et al., 2004; Munch and Werblin, 2006) has not incorporated the robust $GABA_A$-and Cl cotransporter-mediated, directional light responses of SACs. In this poster, we describe in a model how a moving light stimulus can selectively depolarize SAC dendritic tips that point in the direction that the stimulus moves. This provides a possible mechanism for the directional sensitivity of retinal ON-OFF DS ganglion cells. An essential component of this model is the presence of two different types of Cl cotransporter along the length of the SAC dendritic branches, as described in Gavrikov et al., 2006.

2. Introduction: Direction Selectivity



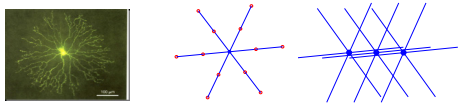
Directionally selective ganglion cells (GCs) respond strongly to light stimuli moving in a particular direction anywhere within their receptive field, but respond little or not at all to stimuli moving in the opposite direction.



- Masland, 2004

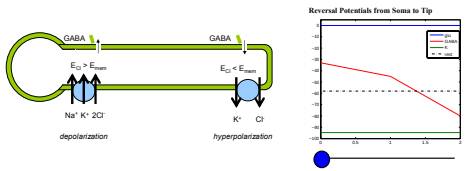
A proposed mechanism is that the SAC dendrites, which are preferentially connected to DS GCs, point in the null direction of the DS GCs (Fried et al., 2002; Gavrikov et al., 2003, 2006; Masland 2004; SACs not drawn to scale). When these SAC dendrites are depolarized by light stimuli moving in the centrifugal direction of the SAC (Euler et al., 2002; Gavrikov et al., 2003, 2006), which is the null direction of the postsynaptic DS GC, they release the inhibitory transmitter GABA onto the DS GC, shunting glutamate excitation from bipolar cells, which also synapse onto the DS GC. Thus in the figure on the right above, the dendritic tips on the right side of the SAC should depolarize more strongly than those on the left side.

3. The Model



A SAC was modeled using a hexagonal array of six dendrites, each with one proximal and one distal compartment. One additional compartment was used to represent the cell soma. Several cells were then synaptically linked together (Lee and Zhou, 2006) as displayed on the right.

Chloride Reversal Potential Determines Polarity of GABA PSPs

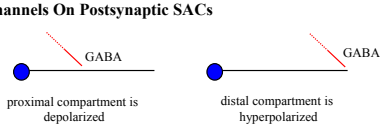


The Cl reversal potential varies along the length of the dendrite due to the presence of one Cl cotransporter (Na-K-2Cl) on the proximal dendrite near the soma and a second type of Cl cotransporter (K-Cl) on the distal dendrite (Gavrikov et al., 2006). Thus a GABA-evoked increase in Cl conductivity depolarizes the proximal dendrites and hyperpolarizes the distal dendritic tip. The figure on the right illustrates the GABA, glutamate, and K^+ reversal potentials (and the resting potential) as a function of SAC dendritic position that were used in the model.

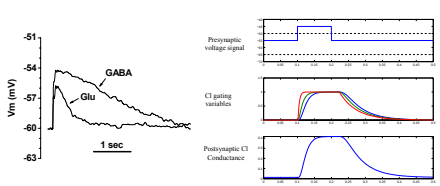
Light Stimuli Induce the Release of Glutamate

Glutamate channels allow the ions Na and K to cross the cell membrane.

Depolarized SAC Dendritic Tips Release GABA Which Opens Cl Channels On Postsynaptic SACs

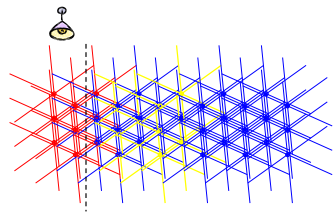


The GABA-evoked Increase in Cl Conductance is Long-lasting



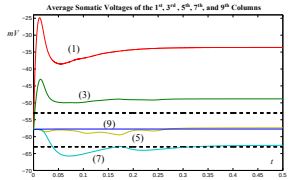
It has been observed experimentally (figure on left) that GABA puffs onto SAC dendrites evoke much longer responses that glutamate puffs (Dmitriev et al., 2007). This phenomenon was modeled using additional dynamical equations for the opening and closing of Cl channels, including two auxiliary gating variables (see model description in No. 7 below for more details).

4. Stationary Stimulus Response



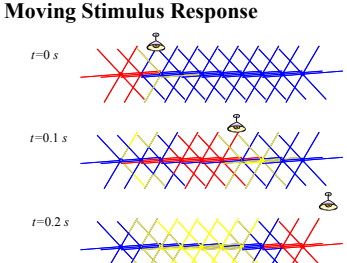
A 12x3 array of SAC cells was stimulated by a constant stationary light stimulus on the left region depicted above. The colors red, blue and yellow represent depolarized, neutral and hyperpolarized dendrites, respectively. The figure illustrates the voltages of the cells and dendrites in the array after the voltages reached a steady state.

Somatic Voltage over Time



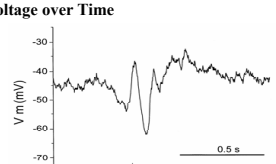
Displayed are the average somatic voltages at various distances from the light signal: Column 1 was under the light stimulus itself. Although the cells in Column 3 were depolarized, the cells in Columns 5 and 7 were increasingly hyperpolarized by the light stimulus. Note that the voltage of Column 9 did not change in this system and that this column lied outside the near periphery of cells in contact with the light stimulus.

5. Moving Stimulus Response



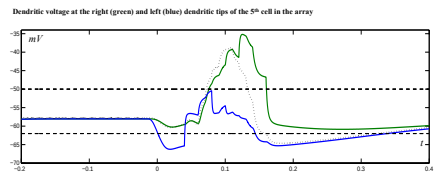
An array of ten SACs was stimulated with a light moving at a speed of 5mm/second (SAC diameter = 0.4 mm). Each cell is slightly rotated for display purposes. The colors red, blue and yellow represent depolarized, neutral and hyperpolarized dendrites, respectively.

Somatic Voltage over Time



The figure above shows the voltage recorded at the SAC soma, using the whole-cell patch-clamp technique, when a light stimulus moved at 5 mm/sec.

Direction Selectivity: Voltage at Left vs. Right Dendritic Tips



Although the voltage at the SAC soma can be monitored, as shown in the previous figure, it is not possible to record the voltage at the dendritic tips of SACs. However, using this parameter set and simulating a light stimulus that moved (5 mm/s) from the left to the right, the model dendritic tips were strongly depolarized on the right side, but not on the left side of the SAC (the somatic voltage is given by the dotted line). The smaller depolarization to motion at the left dendritic tip, compared to the dendritic tip on the right side, is probably the result of the GABA inhibition that precedes and is coincident with the glutamate excitation at the left dendritic tip. In contrast, glutamate and GABA excitation dominate the voltage response at the right dendritic tip. This robust difference in the motion response of the dendritic tips on opposite sides of the SAC can form the basis of direction selectivity.

6. Conclusions

The results of this model, which is based on recent experimental findings (Gavrikov et al., 2006; Dmitriev et al., 2007), suggest that dendritic tips on opposite sides of a SAC produce a DS response to light stimuli that move across the SAC receptive field if:

1. there is an intracellular Cl gradient along SAC dendrites and
2. the response to GABA produces a long-lasting increase in Cl conductance.

Moreover, these modeling results also suggest that signaling between SACs can mediate the DS response of SACs to motion.

7. Model Specification

For every compartment c in a given cell, the dynamics of the voltage $v_c(t)$ at c is given by the equation

$$\tau\frac{dv_c}{dt} = g_{Cl}(E_{Cl}-v_c)+g_{glu}(E_{glu}-v_c)+g_K(E_K-v_c) \quad + \sum_{d \text{ adjacent to } c} c_{couple}(v_d-v_c).$$

The equilibrium potentials $E_{Cl}=E_{Cl}(c)$, E_{Cb}, E_{Cl} depend only on whether c is located at the soma, on a proximal dendrite, or on a distal dendrite.

The glutamate conductance $g_{glu}=g_{glu}(c,t)$ is determined by the formula

$$g_{glu}(c,t) = \begin{cases} g_{glu,bound} \gg 0, & \text{if a light signal is present} \\ g_{glu,rest} & \text{otherwise.} \end{cases}$$

The conductance g_K is a constant parameter of the system.

We now describe the calculation of $g_{Cl}=g_{Cl}(c,t)$. Define $\theta_d(t)$ to be the maximum voltage $v_d(t)$ over all dendritic tips d at the same location as c but different from c. Define auxiliary gating variables $s_{c,2}(t)$, $s_{c,3}(t)$ by

$$\frac{ds_{c,3}}{dt} = \begin{cases} \alpha(1-s_{c,3}), & \theta_c(t) > v_{threshold} \\ -\beta s_{c,3} & \text{otherwise,} \end{cases}$$

$$\frac{\tau_{GABA}}{2}\frac{ds_{c,2}}{dt} = s_{c,3} - s_{c,2}.$$

Define the Cl gating variable $s_{c,1}(t)$ by

$$\frac{\tau_{GABA}}{2}\frac{ds_{c,1}}{dt} = s_{c,2} - s_{c,1}.$$

Finally, let

$$g_{Cl}(c,t) := g_{Cl,rest} + s_{c,1}(t)(g_{Cl,bound} - g_{Cl,rest}).$$

Parameter Values

The following are the parameter values used in this system. For a derivation of reversal potentials and conductance values, refer to (Gravrikov et al 2007).

$E_{glu} = 0mV$; $E_K = -94.7mV$; $c_{couple} = 1$; $\tau = 0.001s$; $E_{Cl,soma} = -33mV$; $E_{Cl,proximal} = -45mV$; $E_{Cl,distal} = -80mV$; $g_K = 1/40(G\Omega)^{-1}$; $g_{glu,rest} = 1/60(G\Omega)^{-1}$; $g_{glu,bound} = 1/6(G\Omega)^{-1}$; $g_{Cl,rest} = 1/72(G\Omega)^{-1}$; $g_{Cl,bound} = 1/2.4(G\Omega)^{-1}$; $\alpha = 250s^{-1}$; $\beta = 20s^{-1}$; $v_{threshold} = -50mV$; $\tau_{GABA} = 0.02s$; SAC diameter: $400\mu m$; light signal speed: $5\ mm/s$; light signal width: $200\mu m$.

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