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Simulation of an Inner Plexiform Layer Neural Circuit in Vertebrate Retina Leads to Sustained and Transient Excitation

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Abstract. The conversion of sustained into transient responses to a step of light in the visual system is first accomplished at the amacrine cells in the vertebrate retina. Neurobiological data from the vertebrate retina have provided some of the key synaptic connections between bipolar and amacrine cells that are thought to underlie the formation of transient and sustained amacrine cell responses to light. Using a neural network model that incorporates data from patch clamp recording techniques in the retinal slice preparation, we have constructed and simulated a connectionist model of the local circuits within the inner plexiform layer of the vertebrate retina that leads to the conversion of sustained to transient excitatory signals similar to those observed in retinal amacrine cells. The model incorporates sustained glutamate release from bipolar cells, $GABA_B$ feedback to bipolar cell axon terminals, $GABA_A$ feedforward input from sustained to transient amacrine cells, and rapidly desensitizing glutamate receptors in the transient amacrine cell.

1. Introduction

Transient and sustained responses to sustained inputs are first developed in the visual system at the level of the inner plexiform layer[1]. Here the excitatory synaptic inputs to the dendritic processes of the transient amacrine cell are brief (relaxation kinetics of T-one-half=100 ms) and those to the sustained amacrine cells are much slower (T-one-half= 800 ms)[2,3]. That the excitatory synaptic currents are different in the two types of amacrine neurons suggests that the neural circuitry underlying the EPSCs (excitatory postsynaptic currents) (mediated by glutamate[4]) of the transient and sustained cells must be different, and that the brief and slow EPSCs of the transient and sustained amacrine cells substantially underlie their differential response properties to a step of light. The voltage responses of the two neurons to a step of light exhibit continuous spiking in the sustained cell and a burst of spikes at light-on and -off in the transient cells[5].

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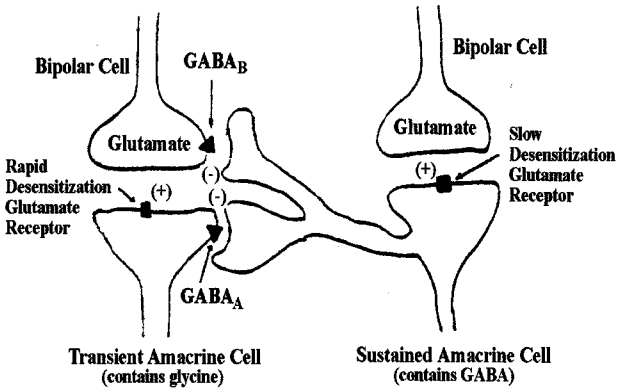

Figure 1: *The neural circuit underlying sustained and transient EPSCs in retinal amacrine cells. The connections are derived from neurobiological data using patch clamp recording methods in the retinal slice preparation.*

2. Circuitry of the Inner Plexiform Layer

The basic circuit underlying the glutamatergic inputs to sustained and transient amacrine cells has been previously described[2,5]. This version of the model incorporates new data that suggests the bipolar cell axon terminal, at least in some cases, releases glutamate in a sustained manner, that transient amacrine cells express rapidly desensitizing glutamate receptors leading to the conversion of a sustained glutamate signal from the bipolar cell into a brief excitation in the transient amacrine cell, and $GABA_B$ feedback to the bipolar cell terminal to inhibit calcium dependent glutamate release during periods where the bipolar cell membrane is at its resting potential. Inhibition of calcium dependent glutamate release from the bipolar cell by $GABA_B$ feedback during periods of rest assures that small amounts of glutamate during the resting phase will not desensitize the rapidly desensitizing component of the glutamatergic EPSC in the transient amacrine cell. Should the $GABA_B$ feedback fail to operate, then the rapidly desensitizing component of the transient amacrine cell response would be lost and all that would remain is the small, slow component of its glutamatergic EPSC. The basic circuit is schematized in Figure 1.

3. Connectionist Model and Simulation Results

Hodgkin and Huxley[6] proposed a model for a patch of membrane using electrical circuit elements. The voltage across a patch of the membrane can be obtained using state equation techniques of the form:

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$$C_m \frac{dV_m}{dt} = -(E_p + V_m)g_p + (E_{Na} - V_m)g_{Na} - (E_K + V_m)g_K, \qquad (1)$$

where C_m is the membrane capacitance, E_K and E_{Na} are the Nernst potentials for potassium and sodium ions, E_p is the Nernst potential for the passive leak current in the membrane, and g_K, g_{Na}, and g_p represent the conductances of potassium, sodium, and passive leak channels respectively.

The following substitutions lead to a shunting equation: $C_m = 1, x_i = E_p + V_m, A_i = g_p, B_i = E_{Na} + E_p, S_i^+ = g_N a$, and $S_i^- = g_K$. The resulting equation is:

$$\frac{dx_i}{dt} = -A_i x_i + (B_i - x_i)S_i^+(t) - (D_i + x_i)S_i(t)^-, \qquad (2)$$

where x_i is the membrane potential (equipotential) of i'th neuron, A_i is the passive decay rate, B_i and D_i the upper and lower bounds of the membrane potential, and S_i^+ and S_i^- are excitatory and inhibitory inputs to the neuron. In general, S_i^+ and S_i^- are a combination of afferent inputs from other neurons and external inputs:

$$S_i^+ = \sum_j w_{ji}^+ f_j(x_j) + I_i^+, \text{ and } \quad S_i^- = \sum_j w_{ji}^- g_j(x_j) + I_i^-, \qquad (3)$$

where w^+ and w^- are excitatory and inhibitory connection weights. The external excitatory and inhibitory inputs are represented by I^+ and I^-. The functions $f_j()$ and $g_j()$ are general nonlinear functions. Because both excitatory and inhibitory terms are multiplied by the cell activity, the model is also called a multiplicative model. A more detailed analysis and discussion of the shunting equations used here can be found in the papers of Öğmen[7-9]. In our neural network, there are 30 neurons. The shunting equations are the essential tool. We also use some other mathematical tools, such as neurotransmitter dynamic model and gated dipole model[7-10]. Here we have modeled the synaptic currents of the amacrine cells, which are nearly proportional to the voltage response in magnitude and opposite in polarity.

3.1. The role of $GABA_B$ feedback to the bipolar cell terminal

Figure 2 shows the simulation results demonstrating the dramatic role that $GABA_B$ feedback plays in shaping the response kinetics of the EPSC in the transient amacrine cell. The source of the GABA mediated feedback is from sustained amacrine cells that are GABAergic[11]. In this model the GABA feedback serves to inhibit the L-type calcium channels found in the bipolar cell axon terminal[10]. This inhibition results in an increase in the threshold in $f_j()$ in equation (3), which is a nonlinear function of the GABA-concentration, and a decrease in the calcium dependent release of glutamate from this terminal. With the GABA feedback present, and with depolarization of the bipolar cell terminal beyond threshold for the L-type calcium channels in the terminal, the concentration of glutamate in the synaptic cleft rises rapidly from near 0 levels to near

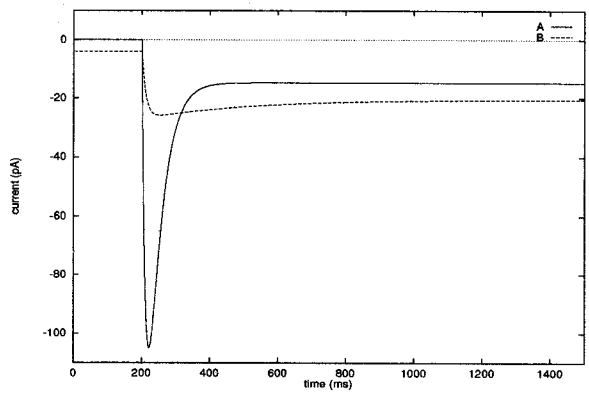

Figure 2: *Simulation of the EPSC in Transient amacrine cell of the vertebrate retina. A) Simulation of the EPSC in transient amacrine cell with inclusion of the GABAergic feedback to the presynaptic bipolar cell axon terminal. B) The same simulation, but without the GABAergic feedback to the presynaptic bipolar cell. The GABAergic feedback pathway is essential for generating the transient EPSC.*

1 mM. This quickly gates the glutamate receptors of the postsynaptic transient amacrine neuron leading to the generation of an EPSC, i.e., the duration of the peak is mainly due to the time constant of the response in the glutamate receptors. Continued depolarization of the bipolar terminal and release of glutamate from the terminal then causes rapid desensitization of approximately 80% of the current (T-one-half= 100 ms). About 20% of the current remains as a slow EPSC. The ratio of the rapid/slow components is variable and may contribute to the variability observed in the light evoked EPSCs of the transient amacrine cells.

3.2. The role of $GABA_A$ feedforward to the transient amacrine cell

$GABA_A$ mediated feedforward inhibition is often, but not always, present in the light evoked responses of transient amacrine cells. Inclusion of the feedforward mechanism in the simulation results in an EPSC as shown in Figure 3. The signal through the bipolar cell → sustained amacrine cell → transient amacrine cell chain occurs after the peak of the EPSC in the transient amacrine cell. The feedforward pathway slightly quickens the relaxation kinetics of the first phase of the EPSC, and reduces in amplitude the second, slow phase of the EPSC. The degree of influence this feedforward pathway exerts in transient amacrine cells is variable, the amplitude of the IPSC (inhibitory postsynaptic current) ranging from not present at all to about 50% of that observed for the EPSC of the same cell.

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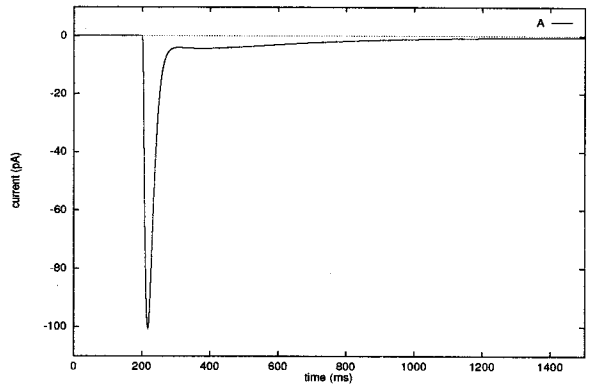

Figure 3: *Simulation of the EPSC in transient amacrine cell with both the feedback GABAergic pathway and feedforward GABAergic pathway. The feedforward pathway increases the transient nature of the response, and reduces the sustained component.*

4. Conclusions

The conversion of the sustained signal in bipolar cells to a brief signal in transient amacrine cells is dependent on a number of factors. Essential factors include pre- and post-synaptic mechanisms at the glutamatergic synapse between bipolar and amacrine cells. Presynaptically, GABA input to bipolar cell axon terminal limits glutamate release onto the amacrine cell during relatively quiescent states and assures prevention of the glutamate receptors in the amacrine cell from reaching a desensitized state. Postsynaptically, glutamate receptors that rapidly gate and rapidly close (rapid desensitization) in the continued presence of glutamate generate a transient EPSC. The relaxation kinetics of the EPSC can be further modified by $GABA_A$ feedforward to the transient amacrine cell and by differential expression of the ratio of rapid/slow components of the glutamate gated ionic current.

Sustained responses in amacrine cells can be generated in amacrine cells even in the presence of rapidly desensitizing glutamate receptors; nonexistence or failure of the $GABA_B$ feedback to the bipolar cell during quiescent states will allow low levels of glutamate to desensitize the rapidly desensitizing glutamate receptors and leave operational only the slowly desensitizing type. In this condition increases in glutamate release will elicit only a slow EPSC in the amacrine cell. An additional means of generating slow EPSCS is to express relatively large numbers of the slowly desensitizing glutamate receptor types. Thus sustained responses in retinal amacrine cells can be generated by the absence of one or both of the essential pre- and post-synaptic glutamatergic mechanisms underlying the transient EPSC. Regulation of these two mechanisms by GABA may very well influence the relaxation kinetics and response properties of the amacrine cells as

has been previously observed [13].

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