Ionic Currents Underlying Difference in Light Response Between Type A and Type B Photoreceptors

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Submitted 22 July 2005; accepted in final form 30 December 2005

INTRODUCTION

Classical conditioning is a universal type of associative learning that is valuable for studying the cellular basis of memory storage. In particular, behavioral and cellular characteristics of classical conditioning in the sea slug, *Hermissenda crassicornis*, are similar to characteristics of mammalian classical conditioning (Lederhendler and Alkon 1989; Matzel et al. 1990). *Hermissenda* learn to associate light, the conditioned stimulus, with turbulence, the unconditioned stimulus, and conductance of calcium-dependent and transient potassium channels. Two additional changes were required to produce a type A photoreceptor model. The very fast firing frequency observed during the first second after light onset required a faster time constant of activation of the delayed rectifier. The fast spike adaptation required a fast, noninactivating calcium-dependent potassium current. Because these differences between type A and type B photoreceptors have not been confirmed in comparative experiments, they constitute hypotheses to be tested with future experiments.

The difference in light-induced activity is explained by several differences in ionic currents. The hyperpolarization activated current, $I_{H}$, has a reversal potential of $-36$ mV in type B photoreceptors versus $-68$ mV in type A photoreceptors (Yamoah et al. 1998). Thus $I_{H}$ maintains the type A photoreceptor at a more negative resting potential and prevents firing in response to dim illumination. Another distinction is that type A photoreceptors have more calcium-dependent potassium current and less transient potassium current than type B photoreceptors (Farley et al. 1990), which may account for the difference in light adaptation.

The type A and type B photoreceptor models were developed in the GENESIS simulation environment (Bower and Beeman 1998) with the costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

The two type A and three type B photoreceptors of the *Hermissenda* eye differ by more than their response to classical conditioning. Type A photoreceptors are silent in low background illumination, whereas type B photoreceptors continue to fire (Alkon and Fuortes 1972). The response to bright light also differs: type A photoreceptors respond with high-frequency firing and then quickly adapt; type B photoreceptors respond with lower-frequency firing, which persists during the light (Alkon and Fuortes 1972; Mo and Blackwell 2003). In other words, both light and dark adaptation are more rapid in type A than in type B photoreceptors.

The type A and type B photoreceptors are correlated with these changes (Alkon et al. 1982, 1985; Farley and Han 1997).

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The light response of the set of five photoreceptors constitutes a spatiotemporal firing pattern that is propagated through the downstream network of interneurons (Crow and Tian 2000, 2002a,b, 2003a,b). Changes in intrinsic currents caused by classical conditioning shape these activity patterns both directly and indirectly by inhibitory interactions among photoreceptors (Alkon and Fuortes 1972; Frysztak and Crow 1994, 1997; Goh and Alkon 1984; Schuman and Clark 1994). The difference in photoreceptor response properties influences inhibitory interactions and thereby shapes spatiotemporal firing patterns that control classical conditioning behavior.

To further understand these spatiotemporal firing patterns, the present study evaluates the currents responsible for the observed differences in light response. The approach is to model the two photoreceptor types and to assess whether the documented differences are sufficient to reproduce experimentally observed differences in light response, or whether additional differences are required.

METHODS

The type A and type B photoreceptor models were developed in the GENESIS simulation environment (Bower and Beeman 1998) with the costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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Differences Between Type A and B Photoreceptors

the Chemesis libraries for modeling calcium dynamics and the second messengers involved in phototransduction. All simulations were run on a Pentium 4 computer running the Redhat Linux operating system. The type B photoreceptor model was developed first; then, the type A photoreceptor model was created by modifying the type B model. Parameter variations were assessed by direct comparison of model simulations with in vitro data.

Parameters were adjusted to reproduce spike characteristics from data in a previous study of the differences between dark-adapted type A and B photoreceptors (Mo and Blackwell 2003). In that study, the circumesophageal nervous system (CNS) was dissected free and incubated with protease to partially dissolve the connective tissue and facilitate micropipette penetration. The CNS was then perfused with artificial seawater containing (in mM): 430 NaCl, 10 KCl, 10 CaCl₂, 50 MgCl₂, and 10 HEPES-Na, adjusted to pH 7.6 with HCl. Photoreceptors were penetrated with potassium acetate–filled aluminosilicate glass micropipettes pulled to a tip resistance of 30 to 40 MΩ. The response to current injection between −0.7 and +0.5 nA was recorded to calculate input resistance, resting potential, and spike characteristics. The response to light was recorded to assess differences in light response and adaptation. Light stimuli had durations between 30 ms and 3 s, and intensities between 1 and 100% of the full intensity of 400 μW/cm². Type A and type B photoreceptors were distinguished by: 1) their typical location within the eye: type A photoreceptors are located rostrally; 2) the cessation of firing immediately after light termination in type A photoreceptors; and 3) characteristic spike height adaptation seen within the first second after light onset in type A photoreceptors.

Action potentials (spikes) of both in vitro and simulated photoreceptors were analyzed using computer programs written in Matlab (The MathWorks). Spike characteristics were analyzed from current injection traces. Spike height is the difference between peak positive deflection and mean steady-state potential arising from current injection. Spike width is the full width at half of the spike height.

Afterhyperpolarization (AHP) amplitude is the difference between mean steady-state potential and peak negative deflection after the spike. AHP min time is the time from peak of the spike to the minimum value of the AHP. To calculate spike frequency in response to light, spikes were detected using a dynamic threshold, calculated as the mean membrane potential plus the minimum expected spike height.

The type B photoreceptor model is based on a previously published model (Blackwell 2002b, 2004), which was modified to include the fast sodium (I_{NaF}) and delayed rectifier potassium currents (I_{KDr}). Parameters of the I_{NaF} equations (Fost and Clark 1996b) were adjusted to match those of the gastropod molluscs, such as Aplysia, which have slower activation kinetics than that of the cephalopod molluscs such as squid (Gilly et al. 1997). Then, the half-activation voltage was shifted by 14 mV to produce a firing threshold similar to that measured in Hermisenda. Figure 1 compares steady-state activation and inactivation of I_{NaF} in the model with those measured in Aplysia. The equations for I_{KDr} were modified from Flynn et al. (2003) with parameters adjusted to reproduce firing frequency in response to somatic current injection. The equations and parameters for these and all ionic currents are listed in the APPENDIX.

The addition of these currents to the previously type B photoreceptor model changed the balance of potassium currents, the calcium influx, and the input resistance of the model. Thus other parameters were modified from the previously published model to reproduce input resistance, spike height and width, AHP amplitude, and firing frequency in response to current injection (I–I curves). The final parameters describing passive properties, ionic currents, and calcium pumps are listed in Tables 1 and 2.

The type A photoreceptor model was created by both sequential and combinatorial changes to the type B photoreceptor model. For each major change (i.e., addition of a current or change in kinetics), dozens of simulations explored the effect of conductance changes. The first set of changes consisted of generally accepted differences between type A and type B photoreceptors. I_{NaF} was inserted into neurite compartments close to the soma; the time constant of I_{NaF} was made faster (Table 3); I_{K} was changed from type B characteristics to type A characteristics (Yamoah et al. 1998; Table 4). The second set of changes was to reduce the transient potassium current (I_{KNa}) and increase the calcium-dependent potassium current (I_{KKCa}). This change is based on voltage-clamp recordings showing a lower I_{KCa} and larger I_{KKCa} in type A photoreceptors (Farley et al. 1990). Many different combinations of maximal conductances (e.g., 8KCa, 8KNa, 8KDr, 8H, 8NaF, 8KCl, 8KCa,KNa) were simulated and evaluated as a part of this set of changes. As described in RESULTS, these changes were not sufficient to reproduce the light response of the type A photoreceptors.

### Table 1. Morphology and passive properties for type A and type B photoreceptor models

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Radius, cm</th>
<th>Length, cm</th>
<th>Calcium Slices</th>
<th>Voltage Slices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soma</td>
<td>10e-4</td>
<td>24e-4</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Neurite</td>
<td>1.5e-4×2.5e-4</td>
<td>100e-4</td>
<td>100</td>
<td>8</td>
</tr>
<tr>
<td>Neck</td>
<td>3e-4</td>
<td>1e-4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Branch (two)</td>
<td>1.2e-4</td>
<td>15e-4</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Rhabomere core</td>
<td>1e-4</td>
<td>12e-4</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Microvill (5,000)</td>
<td>0.04e-4</td>
<td>10e-4</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Electrical properties of the cell are calculated using membrane capacitance = 1 μF/cm², passive membrane resistivity = 0.01 MΩ·cm⁻², and axial resistivity = 0.0004 MΩ·cm·. The membrane resistance of the 5,000 microvill is calculated by assuming only one quarter of the surface area is accessible to the extracellular space. Current flowing across the microvilli membrane flows across an axial resistor consisting of the rhabomere core plus the axial resistance contributed by the 5,000 microvilli. Phototransduction and calcium dynamics are modeled in each of 12 groups of 417 microvilli as in Blackwell (2004).
TABLE 3. Parameters for $\alpha_m$, $\beta_m$, $\alpha_h$, and $\beta_h$ for $I_{NaF}$ (Eqs. A2 and A3)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$m$</td>
<td>0.36</td>
</tr>
<tr>
<td>$\phi$</td>
<td>-47</td>
</tr>
<tr>
<td>$S_m$</td>
<td>-4.5</td>
</tr>
<tr>
<td>$k_m$</td>
<td>-0.4</td>
</tr>
<tr>
<td>$V_{th}$</td>
<td>-56</td>
</tr>
<tr>
<td>$S_p$</td>
<td>20</td>
</tr>
<tr>
<td>$p/q$</td>
<td>3</td>
</tr>
<tr>
<td>$\Theta$</td>
<td>6 (A)</td>
</tr>
</tbody>
</table>

These equations were adapted from Fost and Clark (1996a), to fit data from Gilly et al. (1997) as follows. $V_0$ was shifted by 14 mV; $k_m$ and $S_m$ are the same for both type A and type B; the time constants are slower; $p = 3$, $E_K = 60$ mV.

J Neurophysiol • VOL 95 • MAY 2006 • www.jn.org

The next set of changes was motivated by observations in current clamp. Thus to the extent that they improve the type A photoreceptor model, they constitute testable hypotheses. As described in RESULTS, the time constant of $I_K$, activation was made much faster (Table 4), using a value from the fast end of the range measured in voltage clamp (Acosta-Urquidi and Crow 1995). This produced an earlier AHP in response to current injection and a faster firing rate during light. In addition, to further increase the firing rate in response to light, the activation rate of $I_{NaF}$ was increased. Again, many different combinations of maximal conductances were simulated and evaluated as a part of this set of changes. As described in RESULTS, these changes were not sufficient to reproduce the light response of the type A photoreceptors.

Finally, a fast-activating calcium-dependent potassium current ($I_{KCafast}$) was added to the neurite. This change was required to produce a fast adaptation in response to current injection, while still allowing for an initial phase of high-frequency firing in response to light stimulation. After the optimal type A photoreceptor model was created, additional simulations were performed to further assess the necessity of the potassium current changes, and to better assess the contribution of each of the major changes to the transformation from type B to type A photoreceptor. The effect of each of the major changes is discussed in RESULTS.

RESULTS

The first step in identifying currents underlying the differences between type A and type B photoreceptors was to quantify the differences in response to light and injected current. Some of the differences were reported previously (e.g., Alkon and Fuortes 1972; Mo and Blackwell 2003). Quantitative differences in photoreceptor characteristics, based on the latter study plus additional unpublished data, are reported here. The second step was to develop a type B model that reproduced characteristics of type B photoreceptors recorded in vitro. The third step was to create a type A model by introducing the minimum changes required to reproduce characteristics of type A photoreceptors recorded in vitro.

Type A photoreceptors have larger and faster spikes and AHP than type B photoreceptors

As reported previously, type A photoreceptors have larger action potentials, and larger AHP than type B photoreceptors (Fig. 2, A and B). The significance of this observation was confirmed with a larger data set (Table 5). Additional measurements revealed that type A photoreceptors have narrower spikes, and the time from peak to AHP minimum is smaller than that for type B photoreceptors (Fig. 2, A and B, Table 5). The previously reported correlation between spike height and AHP amplitude of type A photoreceptors disappeared with the larger sample ($R = -0.32$, $P = 0.28$), in part due to one neuron with an exceptionally large AHP. When this neuron is removed, the correlation approaches significance ($R = 0.54$, $P = 0.068$). In addition, for type A photoreceptors (but not type B photoreceptors), spike width is correlated with spike height ($R = 0.69$; $P = 0.009$) and AHP min time ($R = 0.68$, $P = 0.011$).

The response to current injection differs between type A and type B photoreceptors. Some dark-adapted type B photoreceptors, which have stopped firing after 15 min of dark adaptation, produce several spikes with 0.1-nA current injection. In contrast, type A photoreceptors produce no spikes with 0.1 nA, and only one spike with 0.3 nA (Fig. 2C). With higher current injection, type A photoreceptors produce additional spikes, but they adapt very rapidly.
Differences between type A and B photoreceptors

Type A photoreceptors have greater response than type B photoreceptors to changes in illumination

The light response differs significantly between type A and type B photoreceptors. Type A fire much faster than type B during the first second after light onset, but the difference is much smaller thereafter (Figs. 3 and 4A) for both short (30 ms) and long (3 s) duration stimuli. In addition, type A photoreceptors cease firing more quickly after light termination. In short, many aspects of the light response, including light and dark adaptation, are faster in type A photoreceptors than in type B photoreceptors. Light adaptation is best seen in the response to 3-s stimuli as the decrease in firing frequency 1–4 s after light onset. This decrease is much larger in type A than in type B photoreceptors. Dark adaptation is best seen in the response to 30-ms stimuli as the decrease in firing frequency 4–26 s after light onset. Type A photoreceptors cease to fire at this time, whereas type B photoreceptors continue to fire at a rate higher than the dark-adapted frequency.

Type B photoreceptor model emulates response to current injection and light stimulation

The type B photoreceptor model was created by modifying a previously published model (Blackwell 2002b, 2004). To generate action potentials, a fast sodium current $I_{Na}$ was added to neurite compartments 3–8, and a delayed rectifier potassium current $I_{KDr}$ was added to all soma and neurite compartments. In addition, minor modifications were made to the other potassium currents to produce input resistance and action potential characteristics similar to that seen in type B photoreceptors.

Figure 5A illustrates that simulated membrane potential in response to 0.1- and 0.3-nA current injection ($A(t)$) is very similar to that measured experimentally ($A(t)$). Spikes are small and relatively wide, and interspike interval is long. These and other characteristics are compared directly with in vitro photoreceptors in Fig. 2: model characteristics (solid squares) lie within the scatter of in vitro measurements (open squares) in Fig. 2, A–C, demonstrating that spike amplitude and width, AHP amplitude and min time, and $f$–$I$ curves are similar to experimentally measured values. In addition, the 20-MΩ input resistance of the model is within the experimentally measured range of input resistances (23.9 ± 6.4).

This type B photoreceptor model also exhibits light response characteristics similar to experimentally measured type B photoreceptors (Fig. 3; Crow 1985; Mo and Blackwell 2003). Firing frequency during the first second after light onset increases with an increase in intensity, especially for short-duration stimuli (compare Figs. 3 and 6). Firing frequency increases as duration is increased from 30 to 300 ms, but not as duration is further increased to 3 s. The firing frequency between 1 and 4 s after light onset increases with both duration and intensity, with a greater sensitivity to duration, and a smaller sensitivity to intensity compared with initial firing frequency. In both model and in vitro type B photoreceptors, firing continues for a long time after light termination, and also remains sensitive to changes in duration and intensity. These characteristics are summarized in Fig. 4B, which shows mean firing rate during these three periods for light durations of 30 ms and 3 s, both at 100, 10, and 1% light intensity. Comparison of Fig. 4B, left with Fig. 4A, left reveals the similarity between in vitro and model type B photoreceptors.

Three previously identified ionic current differences are not sufficient to distinguish type A and type B photoreceptors

Several key differences between type A and type B photoreceptors have been identified. First, $I_{Na}$ is located in neurite compartments closer to the soma in type A photoreceptors (Farley and Han 1997), producing larger spikes recorded at the soma (Alkon and Fuortes 1972; Mo and Blackwell 2003). Second, the hyperpolarization activated current $I_{K}$ has a lower reversal potential in type A photoreceptors (Yamao et al. 1998). Third, type A photoreceptors have more $I_{KCa}$ and less $I_{K}$ (Farley et al. 1990). If these three differences are not sufficient to explain the different response properties, then additional differences must exist. Identifying and understanding these differences between photoreceptor types is essential for understanding how classical conditioning modifies the spatiotemporal firing patterns produced by photoreceptor interactions.

The first type A photoreceptor model evaluated the hypothesis that the difference between type A and type B photoreceptors is entirely attributed to changes in $I_{h}$ and $I_{Na}$. Thus the type A photoreceptor model was created by making the following changes to the type B photoreceptor model: $I_{Na}$ was

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TABLE 4. Parameters for $X_{K}$ and $x$ for voltage-dependent currents (Eq. A4)

<table>
<thead>
<tr>
<th>Current</th>
<th>$V_{m}$, mV</th>
<th>$S$, mV</th>
<th>$\tau_{m}$, ms</th>
<th>$\tau_{max}$, ms</th>
<th>$V_{m}$, mV</th>
<th>$S$, mV</th>
<th>$E_{K}$, mV</th>
<th>$p$</th>
<th>$q$</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDr, type B*</td>
<td>-12</td>
<td>-11.6</td>
<td>5</td>
<td>150</td>
<td>-38</td>
<td>9.6</td>
<td>-80</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>KDr, type A*</td>
<td>-12</td>
<td>-11.6</td>
<td>5</td>
<td>32</td>
<td>-33.5</td>
<td>10</td>
<td>-80</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>H, type B#</td>
<td>-74</td>
<td>15.5</td>
<td>50</td>
<td>480</td>
<td>-45</td>
<td>-18</td>
<td>-36</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>H, type A</td>
<td>-72</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>-86</td>
<td>-80</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>KA</td>
<td>m</td>
<td>-35</td>
<td>-20</td>
<td>2</td>
<td>4</td>
<td>-23</td>
<td>10</td>
<td>-80</td>
<td>3</td>
</tr>
<tr>
<td>h</td>
<td>-60</td>
<td>8</td>
<td>150</td>
<td>-50</td>
<td>-37</td>
<td>-6</td>
<td>-68</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CaP</td>
<td>m soma*</td>
<td>3.2</td>
<td>-8</td>
<td>150</td>
<td>0</td>
<td>-8</td>
<td>0</td>
<td>-8</td>
<td>0</td>
</tr>
<tr>
<td>m neurite*</td>
<td>13.2</td>
<td>-8</td>
<td>150</td>
<td>0</td>
<td>-8</td>
<td>0</td>
<td>-8</td>
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<tr>
<td>CaT*</td>
<td>m</td>
<td>-30</td>
<td>-10</td>
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<td>0</td>
<td>-8</td>
<td>0</td>
<td>-8</td>
<td>0</td>
</tr>
<tr>
<td>h</td>
<td>-49</td>
<td>6</td>
<td>75</td>
<td>0</td>
<td>-8</td>
<td>0</td>
<td>-8</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*These equations were adapted from Flynn et al. (2003) as follows. Inactivation removed; increased $\tau_{max}$ for type B; decreased $\tau_{max}$ for type A; modification of voltage dependency of both steady state and time constant of activation. # The parameters are identical to those in Blackwell (2004). §Goldman–Hodgkin–Katz equation used to calculate current flow.
added to neurite compartments adjacent to the soma; the time constant of activation for $I_{NaF}$ was decreased; and $I_H$ was changed from the one found in type B photoreceptors to the one found in type A photoreceptors (Tables 2–4). Both this model and one in which $g_{KA}$ is reduced and $g_{KCa}$ is increased (Farley et al. 1990) had very similar action potential and light response characteristics; thus only results from the latter model are described.

These three changes are not sufficient to produce a type A model, as indicated by the lack of resemblance between simulated voltage traces and experimentally measured voltage traces. The characteristics of spikes and AHPs are similar to those measured experimentally, as indicated by the type A model points labeled 1 in Fig. 2; however, the simulated response to light (Fig. 4C, left) does not re-create in vitro measurements. Specifically, the firing rate is too low for all stimulus durations; and insufficient light adaptation is exhibited for 3-s-duration light stimuli. This finding is very robust because many different combinations of conductance densities were evaluated and none produced a light response with reasonable light adaptation (results not shown).

A fast-activating delayed rectifier potassium current is required for the fast firing frequency in type A photoreceptors

The second type A photoreceptor model evaluated the hypothesis that $I_{KDr}$ is faster in type A than in type B photoreceptors. This hypothesis is based on the observation that type A photoreceptors AHPs not only are larger, but also reach their minimum and repolarize faster than those of type B photoreceptors. This hypothesis is supported by voltage-clamp measurements of $I_{KDr}$, which reveal that time-to-peak is between 50 and 90 ms in most type B photoreceptors (Acosta-Urquidi and Crow 1995), whereas the activation time constant of $I_{KDr}$ in type A photoreceptors is $<10$ ms (Farley and Han 1997). To evaluate this hypothesis, type A model 2 was created from type A model 1 by decreasing the time constant of activation of $I_{KDr}$ (Table 4). Additional simulations were performed to find the optimal combination of potassium and sodium conductances to accompany this fast $I_{KDr}$.

Several different combinations of $g_{max}(NaF)$, $g_{max}(KCa)$, and $g_{max}(Kleak)$ all produced good responses to current injection, but poorly adapting light responses. These results are represented using $g_{max}(NaF) = 3.15e5$, $g_{max}(KCa) = 3.0e5$, and $g_{max}(Kleak) = 200$. Spike and AHP characteristics are similar to experimental measurements, as indicated by the type A model points labeled 2 in Fig. 2. On the other hand, although the response to light is much better for model 2 (Fig. 4C, right) than for model 1, light adaptation is still significantly less than observed experimentally (compare with Fig. 4A, right).

### Table 5. Action potential and AHP characteristics differ significantly between type A and type B photoreceptors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type A</th>
<th>Type B</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spike height, mV</td>
<td>46.1 ± 8.9</td>
<td>19.3 ± 3.6</td>
<td>10.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Spike width, ms</td>
<td>3.4 ± 1.1</td>
<td>5.9 ± 1.0</td>
<td>9.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AHP amplitude, mV</td>
<td>−8.5 ± 3.7</td>
<td>−4.0 ± 1.5</td>
<td>4.11</td>
<td>0.001</td>
</tr>
<tr>
<td>AHP min time, ms</td>
<td>16.5 ± 13.9</td>
<td>44.0 ± 14.9</td>
<td>5.31</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 13 for type A, n = 20 for type B.

A fast-activating delayed rectifier potassium current is required for the fast firing frequency in type A photoreceptors

**FIG. 2.** Differences between type A and type B photoreceptors recorded in vitro. Type A photoreceptors indicated by circles; type B photoreceptors indicated by squares. Solid symbols indicate model, open symbols represent in vitro data. A: type photoreceptors have larger and narrower spikes than type B photoreceptors. B: type A photoreceptors have larger and earlier afterhyperpolarizations (AHPs) than those of type B photoreceptors. C: number of spikes in response to current injection is greater for type B than for type A photoreceptors. Model and in vitro points for type A photoreceptors at 0.1 nA, and type B photoreceptors at 0.5 nA, overlap because they are identical. D: changes in spike height, produced by varying the speed (θ) of $I_{NaF}$ in the model, are correlated with changes in AHP amplitude in type A photoreceptors.
cifically, the firing rate from 1 to 4 s is too high for all duration light stimuli, and the firing rate from 4 to 26 s is too high for 3-s stimuli. Increasing (decreasing) the $I_{\text{KCa}}$ conductance decreased (increased) firing frequency at all three time periods, but did not improve light adaptation. Thus these four differences are not sufficient to produce characteristics of type A photoreceptors.

A fast-activating, noninactivating calcium-dependent potassium current is required for the fast spike adaptation of type A photoreceptors.

The main characteristics of type A photoreceptors not observed in either type A model are that light adaptation occurs very quickly after light onset, within 1 to 2 s, and firing in response to current injection ceases even faster, within 200 ms. In addition, light termination is often followed by a hyperpolarization in type A photoreceptors. In many cell types (e.g., Lewis et al. 1986; Sah and Faber 2002), spike frequency adaptation is produced by a calcium-dependent potassium current; however, using the type B $I_{\text{KCa}}$ conductance increases little during current injection (Fig. 7C2), or after the peak of the light response (Fig. 7C1) because the activation time constant ranges from 539 ms under resting conditions ($-55$ mV and 100 nM calcium) to 195 ms under stimulated conditions ($-30$ mV and 400 nM calcium; Fig. 7, A and B). Thus the third type A photoreceptor model was created by adding an additional calcium-dependent potassium current. A faster, calcium-de-
brane potential in response to light of 30-ms, 300-ms, and 3-s durations and 1, 10, and 100% intensity, and portrays key characteristics of the type A photoreceptor light response showed by both the model and in vitro photoreceptors. The firing frequency is very high during the first second after light onset, and increases as duration increases from 30 to 300 ms, but is insensitive to further increases in light duration (Fig. 9A). Similarly, the firing frequency at 300- and 3,000-ms stimuli saturates at 10% intensity, as observed experimentally (cf. Fig. 7A of Mo and Blackwell 2003). The simulated firing frequency between 1 and 4 s after light onset drops to zero for 30-ms-duration stimuli, and is >10 Hz lower than the firing frequency during the first second for 300-ms- and 3-s-duration light stimuli. Although the response to 30-ms stimuli is lower than the experimentally observed mean value (Fig. 9B), the latter was highly variable, and more than half of recorded type A photoreceptors did not fire between 1 and 4 s after light termination in response to 30-ms stimuli. The time of last spike for type A photoreceptors is strongly dependent on light duration and slightly dependent on intensity. These characteristics are summarized in Fig. 9, which illustrates firing frequency from 0 to 1 s (A), firing frequency from 1 to 4 s (B), and time of last spike (C) for three durations and two intensities of light stimuli, and presents the mean and SE of in vitro measurements for comparison.

Additional simulations were performed to further assess the role of $I_{KCfast}$ and to demonstrate some of the essential features of this current. First, to test the necessity of a fast calcium-dependent potassium current, $I_{KCfast}$ in the neurite was replaced by the slower $I_{KCa}$ added to the neurite. This type A model had a slower initial spike rate and less spike adaptation, similar to model 2 (results not shown); thus $I_{KCfast}$ is required to produce spike adaptation similar to that of in vitro photoreceptors. Second, to test the necessity of locating a calcium-dependent potassium current in the neurite, $I_{KCfast}$ was removed from the neurite and added to the soma. This type A model had a good initial spike rate and spike adaptation in response to 100% intensity stimuli, but the spike adaptation in response to 10 and 1% intensity stimuli was less than that observed experimentally. In conclusion, $I_{KCfast}$ located in the neurite is required to reproduce the fast spike adaptation observed in type A photoreceptors recorded in vitro.

Yet other simulations were performed to assess the necessity of a fast delayed rectifier current. The fast $I_{Kdr}$ was replaced with the type B delayed rectifier current, and simulations were repeated, both in the optimized type A photoreceptor model, and in models with 1) reductions in various potassium conductances, 2) modified transient potassium channel parameters, and 3) increased conductance of the fast sodium current. None of these models was able to reproduce the fast action potential firing observed in type A photoreceptors (results not shown); thus a fast delayed rectifier is required to produce firing characteristics of type A photoreceptors in vitro.

**DISCUSSION**

The objective of the study was to identify the differences in ionic currents that completely characterized the differences in response properties of type A and type B photoreceptors. The approach was to develop a type B model that reproduced characteristics of type B photoreceptors recorded in vitro, and then to create a type A model by sequential changes to membrane currents that have been experimentally documented, accompanied by combinatorial explorations of conductance parameters. Necessary and sufficient differences were identified by comparison of the various type A models with characteristics of type A photoreceptors recorded in vitro.

The results showed that five main differences were required, three of which have been characterized experimentally and two of which constitute hypotheses to be tested with comparative experiments in the future. The three differences between type A and type B photoreceptors that are characterized experimentally include $I_{H}$: activation time constant and location of $I_{Na}$; and conductance of $I_{KCa}$ and $I_{KA}$. Including the type A versions...
of these currents into the type B photoreceptor model transformed the action potential and AHP characteristics of the model, but did not adequately reproduce the light response. Two additional changes, with modest experimental support, were required to produce a type A photoreceptor model. The very fast firing frequency observed during the first second after light onset required a faster time constant of activation of $I_{KDr}$. The fast spike adaptation in response to light and current injection required a fast, noninactivating calcium-dependent potassium current, such as $I_{KCaFast}$. These latter differences between type A and type B photoreceptors constitute hypotheses to be tested with future comparative experiments.

The requirement for a fast $I_{KDr}$ does have some experimental support, in that voltage-clamp recordings from type B photoreceptors reveal a wide range of activation time constants, with peak times between 12 and 90 ms (Acosta-Urquidi and Crow 1995). Most of the photoreceptors had the slower activation time constants, but the fast end of the range demonstrates that a fast-activating $I_{KDr}$ exists in the *Hermissenda* eye. Furthermore, voltage-clamp studies of type A photoreceptors (Farley and Han 1997) reveal that $I_{KDr}$ in these cells is fast, with activation time constants $<10$ ms. Nonetheless, definitive support for the hypothesis that the activation time constant of $I_{KDr}$ differs between type A and type B photoreceptors requires a comparative study, to ensure that methodology does not account for the observed differences.

The requirement for a fast-activating, noninactivating calcium-dependent potassium current to produce spike frequency adaptation is consistent with properties of calcium-dependent potassium currents in other neurons, both vertebrate (e.g., Sah and Faber 2002) and invertebrate (e.g., Lewis et al. 1986). Calcium-activated potassium channels constitute several subtypes. SK channels are strictly calcium dependent and sensitive to apamin; BK channels are voltage and calcium dependent and are blocked by paxalline, charybdotoxin, and iberiotoxin. Importantly, $\beta$ subunits of BK channels control gating kinetics

**FIG. 5.** Membrane potential in response to current injection are similar for model and in vitro measurements. A: type B photoreceptor model (A1) and in vitro recordings (A2) in response to 0.1 and 0.3 nA. B: type A photoreceptor model (B1) and in vitro recordings (B2) in response to 0.3 and 0.5 nA. Traces are offset arbitrarily for display purposes.

**FIG. 6.** Light response of type B photoreceptor model is similar to that measured experimentally. A: 3 s duration stimuli. B: 300 ms duration stimuli. C: 30 ms duration stimuli. 1, 10, and 100% refer to light intensity. Bar beneath the traces indicates light time course. Compare with Fig. 3 of Mo and Blackwell (2003).
(Moss et al. 1999; Nimigean and Magleby 2000; Ramanathan et al. 2000); thus a diversity of β subunits translates into a diversity of calcium sensitivities and time constants.

Although the specific subtype of calcium-dependent potassium channel has not been determined in *Hermissenda*, the voltage dependency of \( I_{\text{KCa}} \) (Sakakibara et al. 1993) suggests that *Hermissenda* have BK channels. This is consistent with the presence of BK channels in a related mollusc, *Aplysia* (Zhang et al. 2002). The fast time constant of activation of the paxilline-sensitive current in *Aplysia* is indirect support for the existence of a fast calcium-dependent potassium current in *Hermissenda*. In addition, one study of potassium currents in the soma of type A photoreceptors (Farley and Han 1997) shows a calcium-dependent potassium current with activation time constant \( \tau_a \approx 100 \text{ ms} \) and with no inactivation.

Aside from the experimental evidence, the simulation evidence for a second type of calcium-dependent potassium current is rather compelling: removing the neurite \( I_{\text{KCaFast}} \) and either increasing the soma \( I_{\text{KCa}} \) or placing the slower \( I_{\text{KCa}} \) in the neurite produces a type A model that fires either too slowly during the light, or has insufficient spike adaptation, depending on the maximal conductance of these currents. On the other hand, these simulations do not indicate the exact characteristics of the hypothesized \( I_{\text{KCaFast}} \); other combinations of parameter values may suffice so long as activation is relatively fast and no inactivation occurs. Thus experiments are required to test the model prediction that type A photoreceptors possess a calcium-dependent potassium current faster than observed in type B photoreceptors, and to evaluate its parameters.

A previous model of type A and type B photoreceptors (Fost and Clark 1996a,b) used different light induced sodium currents and \( I_{\text{NaF}} \) for the type A model compared with the type B model. In the present model, changes in the \( I_{\text{NaF}} \) time constant produced a larger and narrower spike, and the faster activation of the light-induced sodium current produced a small increase in the initial firing frequency; however, neither of these changes had a major effect on spike adaptation. Similarly, the faster activation time constant of the type A photoreceptor light

### Table 6. Parameters for calcium-dependent potassium currents (Eq. A7)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>minV</th>
<th>maxV</th>
<th>( V_{\text{th}} ) (mV)</th>
<th>( S_{\text{th}} ) (mV)</th>
<th>( m_{\text{SS}} )</th>
<th>( h_{\text{SS}} )</th>
<th>( C_{\text{Ca0}} ) (log mmol)</th>
<th>( S_{\text{C1}} ) (log mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( m_{\text{SS}} )</td>
<td>0</td>
<td>1</td>
<td>-34</td>
<td>-17</td>
<td>0</td>
<td>1</td>
<td>-4.15</td>
<td>-0.6</td>
</tr>
<tr>
<td>( \tau_{\text{m}} )</td>
<td>310</td>
<td>425</td>
<td>-33</td>
<td>4</td>
<td>0.167</td>
<td>0.83</td>
<td>-3.69</td>
<td>0.4</td>
</tr>
<tr>
<td>( h_{\text{SS}} )</td>
<td>0.3</td>
<td>0.7</td>
<td>-36</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>-3.6</td>
<td>0.11</td>
</tr>
<tr>
<td>( \tau_{\text{a}} )</td>
<td>1,000</td>
<td>1,200</td>
<td>-10</td>
<td>-5</td>
<td>0.22</td>
<td>0.78</td>
<td>-3.5</td>
<td>-0.7</td>
</tr>
<tr>
<td>( \tau_{\text{a}} ) (KCafast)</td>
<td>200</td>
<td>50</td>
<td>-33</td>
<td>4</td>
<td>0.7</td>
<td>0.3</td>
<td>-3.69</td>
<td>0.4</td>
</tr>
<tr>
<td>( h_{\text{SS}} ) (KCafast)</td>
<td>0.3</td>
<td>0.7</td>
<td>-36</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Units of \( m_V \) and \( m_h \) are in milliseconds for \( \tau \). \( E_R = -85 \text{ mV} \).
induced sodium current produced a small increase in the firing frequency, but had little effect on light or dark adaptation. The Fost and Clark model did not include differences in the delayed rectifier or calcium-dependent potassium currents, most likely because they were not attempting to reproduce firing frequency for a wide range of light stimuli.

In addition to the differences in firing frequency, in vitro measurements reveal that type A photoreceptors have a smaller peak generator potential in response to low illumination and a larger peak generator potential (about 5 mV) in response to high illumination (cf. Fig. 5, Mo and Blackwell 2003). Thus phototransduction in type A photoreceptors appears to be less sensitive, but with a slightly greater capacity. The latter could be attributable either to a larger maximum conductance of $I_{\text{NaLgt}}$ or to a higher input resistance. Given the 32-nS conductance of $I_{\text{NaLgt}}$ (Blackwell 2002a) and 24-MΩ input resistance of type B photoreceptors, the increase in peak generator potential of type A photoreceptors can be produced by an approximately 10% increase in either input resistance or conductance. The difference in sensitivity may arise from the light-induced sodium current or upstream signaling events in the phototransduction cascade. Differences in signaling events could include rhodopsin sensitivity, affinity of phospholipase C for its G-protein α subunit, or calcium dynamics. In vertebrates, the difference in sensitivity between rods and cones is primarily attributed to differences in calcium dynamics (Miller et al. 1994). The modicum of experiments on *Hermissenda* phototransduction (Sakakibara et al. 1994, 1998) and calcium dynamics (Ito et al. 1994; Muzzio et al. 1998) makes modeling these differences fraught with uncertainties.

Previous models of *Hermissenda* photoreceptors (Cai et al. 2003; Flynn et al. 2003; Fost and Clark 1996a,b) characterize how changes in ionic currents, caused by serotonin or classical conditioning, produce changes in type B photoreceptor excitability and synaptic interactions. These studies demonstrate that decreases in $I_{\text{KCa}}$ predominantly increase the plateau firing frequency, whereas changes in three other currents, $I_{\text{KA}}$, $I_{\text{H}}$, and $I_{\text{Ca}}$, predominantly influence neurotransmitter release, by an increase in spike width and calcium influx. The most significant difference with those prior models is that the present model includes biochemical reactions underlying phototrans-
duction and multiple mechanisms governing calcium dynamics. This more accurate model allows reproduction of a broader range of physiological characteristics of in vitro photoreceptors. A logical next step would be to use these photoreceptor models to confirm the findings in those studies and to further investigate the changes in spatiotemporal firing patterns produced by classical conditioning.

The study was motivated by the need to understand how inhibitory interactions between the photoreceptors (Alkon and Fuortes 1972; Frystak and Crow 1994, 1997; Goh and Alkon 1984; Schuman and Clark 1994) shape the activity patterns propagated through the downstream network of interneurons (Crow and Tian 2000, 2002a,b, 2003a,b). The high firing frequency of type A photoreceptors after the first second after light onset and the low input resistance caused by the photocurrent suggest that inhibitory interactions from type B cells are shunted. In contrast, after the initial light response, during the plateau that occurs with light stimuli >1 s, type B photoreceptors fire as fast as type A photoreceptors, in part as a result of inhibition of type A photoreceptors, and in part as a result of rapid spike adaptation. Thus the spatiotemporal firing pattern during light in untrained *Hermissenda* consists of two of the five photoreceptors firing at a frequency significantly higher than the other three, followed by all five photoreceptors firing at a medium frequency.

More important is the desire to understand how classical conditioning changes the output of the five photoreceptors of the eye. In other words, changes to photoreceptor intrinsic currents and synaptic interactions caused by classical conditioning ultimately produce a change in behavior. Although inhibitory synaptic inputs to type A photoreceptors are probably shunted during the first second after light onset, the increase in *I*\textsubscript{KDr} and smaller generator potential arising from classical conditioning (Farley and Han 1997; Frystak and Crow 1993) may produce a smaller initial firing frequency of type A photoreceptors, creating a more uniform firing frequency across the set of five photoreceptors. After the first second of light response, the increased firing frequency of type B and inhibition of type A by type B photoreceptors ascribed to classical conditioning, coupled with the increase in *I*\textsubscript{KDr}, may dramatically reduce the type A photoreceptor firing, resulting in three of the five photoreceptors firing at a significantly higher rate than that of the other two.

The inhibitory interactions between type B photoreceptors may produce a more dramatic change in the temporal pattern of activity. Both an increase in variability of interspike interval (Crow 1985) and periodic burst firing (Mo and Blackwell 2003) are seen after classical and in vitro conditioning. Periodic burst firing patterns are seen in many systems, including networks with mutually inhibitory interactions and sustained excitatory inputs (Chen et al. 1998; Popescu and Frost 2002). In *Hermissenda*, tonic excitatory input to the mutually inhibitory type B photoreceptors is provided by light stimulation. Periodic bursting may develop after classical conditioning because both strength and persistence of neuronal synaptic interactions influence the occurrence and characteristics of periodic activity (Ermentrout 2003; White et al. 2000). One possibility that can be explored with network simulations, is that the increase in firing frequency coupled with an increase in inhibition produces oscillatory firing patterns in the type B photoreceptors. Of compelling interest is how this change in spatiotemporal firing pattern is propagated through the neuronal network to produce a change in motor behavior in response to light.

**APPENDIX**

All voltage-dependent ionic currents were modeled using the same general form of equations

\[
I = g_{\text{max}} h m^2 (V_m - E_\text{rev}) \text{ d}X = \frac{X - X_{SS}(V_m)}{\tau} \tag{A1}
\]

where \(X\) indicates either \(m\) (the activation variable) or \(h\) (the inactivation variable). For currents without inactivation, \(q = 0\). \(X_{SS}\) and \(\tau\) are specified either directly (as a voltage-dependent function) or they are given as functions of \(\alpha\) and \(\beta\).

**Fast sodium current (I\textsubscript{NaP})**

\(X_{SS}\) and \(\tau\) are functions of \(\alpha\) and \(\beta\)

\[
X_{SS} = \frac{\alpha}{\alpha + \beta} \text{ and } \tau = \frac{\Theta}{\alpha + \beta} \tag{A2}
\]

\[\alpha \text{ or } \beta_m = \frac{k(V - V_0)}{1 - \exp\left(\frac{V - V_0}{S}\right)} \quad \beta_h = \frac{k_m}{1 + \exp\left(\frac{V - V_{0m}}{S_m}\right)} \tag{A3}\]

Parameters are given in Table 3. The parameter \(\Theta\) in Eq. A2 is equivalent to, but simpler than, including this parameter in the numerator of both \(\alpha\) and \(\beta\) in Eq. A3. A larger \(\Theta\) produces a slower rate of activation or inactivation.

**Voltage-dependent (delayed rectifier) potassium current (I\textsubscript{KDR})**

\(X_{SS}\) and \(\tau\) are given directly

\[
X_{SS} = \frac{1}{1 + \exp\left(\frac{V - V_r}{S}\right)} \text{ and } \tau = \tau_{\text{max}} + \frac{\tau_{\text{max}}}{1 + \exp\left(\frac{V - V_0}{S}\right)} \tag{A4}\]

Parameters are given in Table 4.

**Hyperpolarization activated current (I\textsubscript{H})**

\(X_{SS}\) and \(\tau\) are given directly. Parameters are given in Table 4.

**Transient potassium current (I\textsubscript{KA})**

\(X_{SS}\) and \(\tau\) are given directly for both \(m\) and \(h\). Parameters are given in Table 4.

**Transient and persistent calcium currents (I\textsubscript{CaP}, I\textsubscript{CaT})**

\(X_{SS}\) and \(\tau\) are given directly for both \(m\) and \(h\). Parameters are given in Table 4.

**Leak potassium current (I\textsubscript{Kleak})**

The leak potassium current was modified slightly from that given in Blackwell (2004). The fraction of open channels for the potassium leak current is obtained by solving the following set of equations for \(m\); both \(m_h\) and \(m_s\) are closed states of the channel


**Table A1. Parameters for ligand-gated currents (Eqs. A5 and A6)**

<table>
<thead>
<tr>
<th>Current</th>
<th>(k_{1p}) ms(^{-1}) mol(^{-2})</th>
<th>(k_{1r}) ms(^{-1})</th>
<th>(k_{2p}) ms(^{-1}) mol(^{-2})</th>
<th>(k_{2r}) ms(^{-1})</th>
<th>(E_{R}) mV</th>
<th>(p)</th>
<th>(q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K(_{leak})</td>
<td>2e(-3)</td>
<td>1.2e(-3)</td>
<td>20e(-3)</td>
<td>0.1e(-3)</td>
<td>(-85)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Na(_{L}) type B*</td>
<td>2e(-3)</td>
<td>10e(-3)</td>
<td>6e(-3)</td>
<td>0.5e(-3)</td>
<td>30</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Na(_{L}) type A</td>
<td>3e(-3)</td>
<td>15e(-3)</td>
<td>6e(-3)</td>
<td>0.5e(-3)</td>
<td>30</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Parameters are the same as those in the previous model.

\[
\frac{dm}{dt} = k_1 m_0 (1 - m_0) \quad (A5)
\]

Parameters are given in Table A1.

**Light-induced sodium current (I\(_{Na,leak}\))**

The fraction of open channels is obtained by solving the following for \(m\) and \(h\):

\[
\frac{dm}{dt} = k_1 [IP]_0 - m [IP]_0 + k_{1} \quad (A6)
\]

\[
\frac{dh}{dt} = (-k_1 [IP]_0 - k_3 h) + k_2
\]

Parameters are given in Table A1.

**Calcium-dependent potassium current (I\(_{KCa}\) and I\(_{KCa,fast}\))**

The calcium-dependent potassium current was modified slightly from that given in Blackwell (2004). The general form of the equation is similar to that of the voltage-dependent currents, except that voltage-dependent steady states and time constants are multiplied by calcium-dependent terms.

\[
X_{ss} = \frac{\text{min}_1 + \frac{\text{max}_1}{1 + \exp\left(\frac{V - V_{1/2}}{S_1}\right)}}{1 + \exp\left(\frac{\log(Ca) - C_{01}}{S_0}\right)} \quad (A7)
\]

Table 6 lists the parameters for steady states and time constants for both activation and inactivation. For both KCa currents, \(p = 3\), \(q = 1\), \(E_{R} = -85.0\).

**Acknowledgments**

I am grateful to J-L. Mo for additional measurements of photoreceptor action potentials and to S. Nayak for a preliminary version of action potentials in the type B model.

**Grants**

This work was supported by National Science Foundation Grant IBN0075909.

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