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Cellular basis of the photoresponse of an extraretinal photoreceptor*

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The sensory physiology of photoreception has largely dealt with the response mechanisms of highly complex eye organs. Most of these systems subserve visual functions for the whole animal and consist of very specialized arrays of both neuronal and nonneuronal cells. It has long been known, however, that certain, often subtler, responses to light occur and that many of these are independent of the visual apparatus. Several recent reviews have revealed a wide range of responses linked to these extraretinal photoreceptors including primitive protective reactions and diurnal regulation of rhythms in locomotor activity and hormone levels[1-4]. The transduction process is uncertain in retinal photoreceptors, there being 2 schools of thought: one holding that calcium release is the basic event[5], the other that a reduction in cyclic GMP is primary[6,7]. In extraretinal photoreceptors the transduction process has been established with more certainty[8] and the theory and supporting evidence are reviewed in this paper.

We used as our experimental object, identifiable neurons from the marine gastropod *Aplysia californica.* The central nervous system of *Aplysia* contains a number of orange-red pigmented neurons[9,10] and it was shown years ago that the electrical activity of some of these neurons is altered by flashes of light[9]. The photoresponsiveness was long associated with the presence of pigmented cytoplasmic granules called lipochondria by Arvanitaki and Chalazonitas[9]. In this review we present data on the photoresponse mechanisms of 2 identifiable *Aplysia* neurons but it is likely that the results and theory to which they are matched apply generally.

Two large (150–300 μm in diameter) identifiable neurons show similiar responses to light differing only in their absolute sensitivities. Both neurons are located in the abdominal ganglion: the dorsal 'giant' neuron, R_2[10] and the ventral photoresponsive neuron (VPN)[8,11]. Our initial studies were electrophysiological although morphological and biochemical correlates were done subsequently. Both neurons hyperpolarize in response to illumination and show similar spectral sensitivities. The response mechanism of VPN will be discussed primarily and, where relevant, comparisons will be made with R_2.

In the dark VPN is generally spontaneously active with a discharge rate of 60–70 spikes per min (fig. 1). A brief flash of light results in an inhibition of firing and a hyperpolarization of the membrane which lasts for many sec. The response develops slowly with a latency of 300–500 msec and a time to peak of 5–10 sec. Following the peak hyperpolarization the membrane potential returns to resting levels within 30–60 sec and VPN begins to spike spontaneously again. Using the voltage clamp technique and holding the membrane potential at −50 mV, near its normal resting level, a light flash evokes an outward current and an increase in membrane conductance (fig. 1). Action spectra for the photoresponses of both VPN and R_2 show similar relationships with a single, broad peak at between 470 nm and 490 nm (fig. 2) and with effectiveness dropping rapidly at shorter or longer wavelengths[8,12]. These action spectra resemble the absorption maxima of molluscan rhodopsins[13].

Voltage clamp studies of the light-induced current vs voltage relationships for both VPN and R_2 showed reversal potentials for the light-induced current of between −70 and −80 mV (fig. 3)[8,14]. This corresponds closely to the equilibrium potential for potassium ion measured in R_2[15,16]. Alterations in the external potassium ion concentration resulted in shifts in the photocurrent-voltage relationship similar to those predicted by the Nernst relationship for potassium ion (fig. 3). Alterations in external Na^+ or Cl^- did not affect the photoresponse[12]. Thus the light-induced conductance increase is selective for potas-

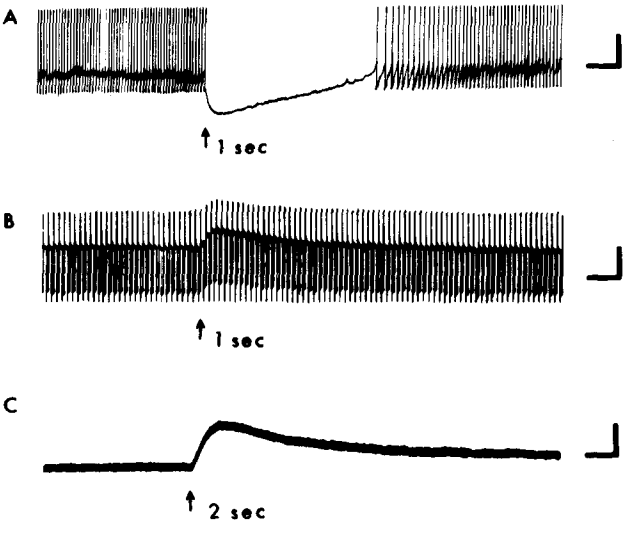

Figure 1. *A* Hyperpolarizing response elicited by illumination of VPN. The spontaneous discharge of 60 spikes/min was interrupted by a 1-sec light stimulus at the arrow. The average interspike membrane potential was −48 mV. Calibration bars: 20 mV, 10 sec. *B* Voltage-clamped VPN current responses to command voltage steps which hyperpolarized the membrane by 10 mV. The 1-sec light stimulus (arrow) increased membrane conductance. Inward current transients are attenuated at bottom. Holding potential was −50 mV. Calibration bars: 1 nA, 10 sec. *C* Outward membrane current response of VPN produced by a 2-sec light stimulus (arrow). Holding potential was −50 mV. Calibration bars: 1 nA, 10 sec. (From Andresen and Brown, 1979.)[8]

sium ion. The light-induced current persisted, however, in the presence of tetraethylammonium chloride (TEA), which blocks the late, voltage-dependent outward potassium current[17] or in the presence of rubidium ion, a blocker of the inwardly rectifying potassium conductance[18]. The results are consistent with a calcium-activated potassium channel known to be present in these neurons[19]. Hence we proposed the theory that phototransduction was mediated by calcium release[12]. Support for this came from the following observations. In R_2 injection of buffer-controlled amounts of calcium (fig. 4) using the calcium chelator, ethylene glycol-bis-(aminoethylether)-N, N^1-tetra-acetic acid (EGTA) produces graded changes in potassium conductance which mimick the light response[14]. On the other hand injection of EGTA alone prevents the light response. We can conclude that changes in intracellular calcium activites are importantly involved. The intracellular calcium transient probably requires that calcium be released from stores since removal of extracellular calcium or addition of cobalt ions to the extracellular fluid does not alter the light response[8,14]. Further support for this view comes from the findings that cooling greatly attenuates or abolishes the light-induced current[8,14]. At 5 °C, injection of calcium, however, produces an increase in membrane conductance which persists until the neuron is rewarmed (fig. 4). To summarize the light-induced increase in potassium conductance is due to an illumination-associated rise in intracellular calcium which does not depend on extracellular calcium sources but does require an active recovery process within the cell to return intracellular calcium to low levels. Where are the photopigment and the calcium involved in the light response located? This is discussed in the next section.

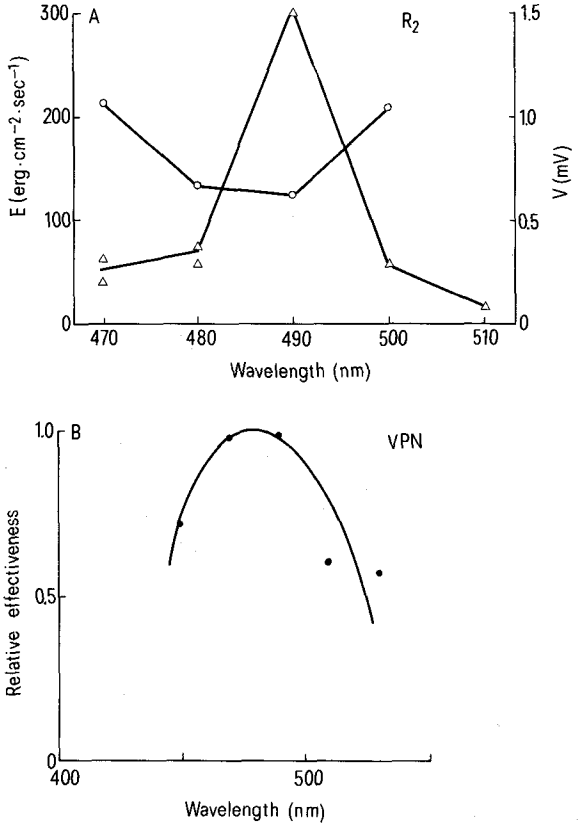

Figure 2. Action spectra for the electrophysiological responses of R_2 and VPN to illumination. *A* R_2: the circles and left ordinate show the relationship of the energy required to elicit a criterion, light-induced current response of 0.3 nA vs wavelength. The triangles and the right ordinate plot the relationship of the magnitude of the light-evoked hyperpolarization vs wavelength for equal energy light flashes. *B* VPN: filled circles show the relative effectiveness of equal quanta of light of various wavelengths. For details, see Andresen and Brown[8]. (Adapted from Brown and Brown, 1973, and Andresen and Brown, 1979)[12,8].

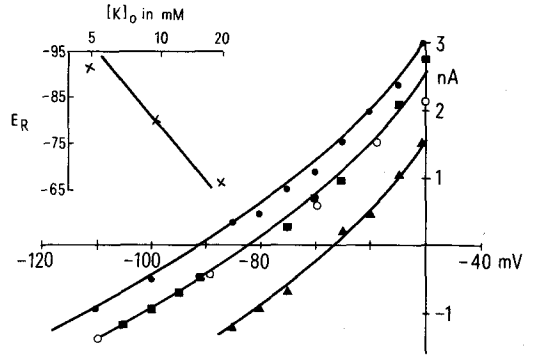

Figure 3. Plot of the net light-induced current (I_L) elicited by second step in voltage away from a holding potential of −50 mV at the peak of I_L for VPN. Neuron was perfused in cobalt-containing artificial seawater with different potassium (K) concentrations. Filled squares, normal 10 mM KCl. Filled circles, 5 mM KCl. Filled triangles, 20 mM KCl. Open circles represent current predicted by constant field equation for a normal distribution of K[15,16]. Continuous lines are fit by eye. Inset shows plot of reversal potential (E_R) vs external potassium concentration $[K]_O$ for I_L-V curves. Continuous line is predicted Nernst relationship for K[8].

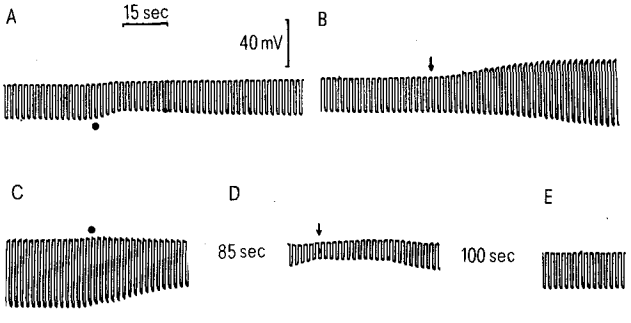

Figure 4. Effects of cooling upon the response of R_2 to intracellular injection of calcium (10^{-11} L of 0.3 M Ca Cl_2). Tracing shows the voltage deflections produced by hyperpolarizing constant current pulses. Resting membrane potential was −60 mV. *A* At 22 °C calcium was injected intracellularly at dot resulting in a transient increase in membrane conductance. *B* At the arrow, cooling the neuron to 5 °C depolarized the membrane and increased the membrane resistance. *C* Injection of calcium (dot) at 5 °C increased membrane conductance. *D* After 85 sec, the changes in membrane potential and conductance were maximal and persistent until the neuron was rewarmed (arrow). *E* After 100 sec at 22 °C the membrane potential and conductance had recovered. (From Brown et al., 1977.)[14]

Intracellular location of the photopigments and calcium

The cytoplasm of many *Aplysia* neurons including VPN and R_2 contains large numbers of pigmented organelles termed lipochondria[9-11]. Microanalysis shows that the pigments are found preferentially in the lipochondria with little free in the cytoplasm and microspectrophotometry of individual lipochondria show absorption spectra similar to the action spectra for the photoresponse (fig. 5)[20]. Chromatographic, spectrophotometric, and resonance Raman spectroscopic studies indicate that isolated lipochondria and their extracts contain at least 2 pigments, β-carotene and a compound that appears to be retinol (fig. 5)[21-23]. Lipochondria also contain calcium at a concentration of 10^{-1}-10^{-2} M (Krauhs et al.)[22] and thus appear to fulfill the basic requirements for a cytoplasmic organelle subserving these photoresponses we have described - they contain both chromophore and calcium stores.

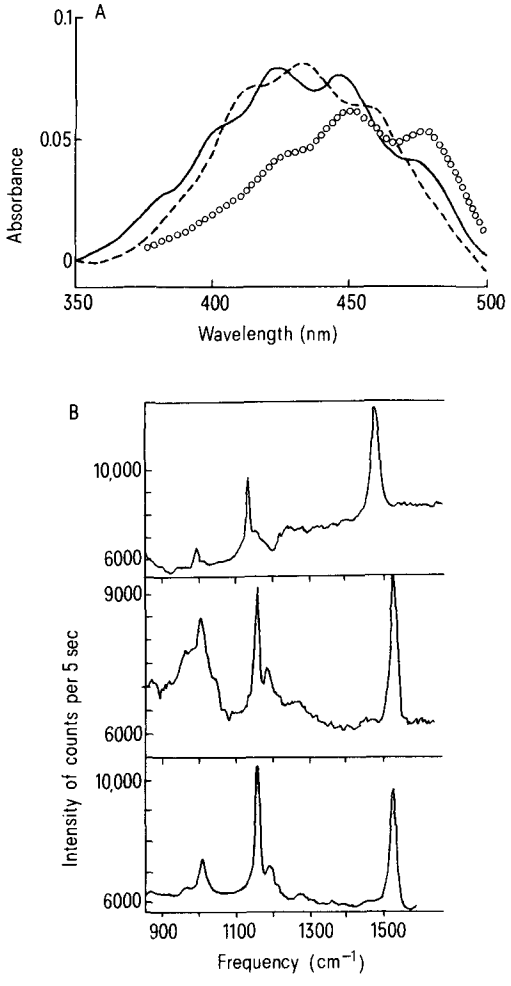

Figure 5. Absorption and resonance Raman spectra for lipochondria and extracts. *A* Absorption spectra of isolated lipochondria (dashed line) a petroleum ether extract of the lipochondrial pigment (solid line) and β-carotene in petroleum ether (filled circles). Absorbance range on the ordinate is 0 to 0.1 A. *B* Resonance Raman spectroscopy of isolated lipochondria (top), a petroleum either extract of the lipochondrial pigment (middle) and β-carotene in petroleum ether (bottom). (Courtesy of Dr. A. Lewis.)

Under an illumination protocol similar to the electrophysiological experiments, lipochondria undergo graded morphological changes[24,25]. In the dark adapted state lipochondria appear predominantly in the globular form with a single limiting membrane and moderately electron opaque ground substance (fig. 6). Following exposure to light, increasing numbers of lipochondria appear first to be mottled with lower light intensities and then, with high intensities, to be converted to a complex lamellar form featuring paracrystalline arrays of membrane-like layers within each lipochondrion (fig. 6). X-ray microprobe analysis of lipochondria before and after light treatment (fig. 6) show that the ultrastructural changes produced by illumination are accompanied by substantial losses in lipochondrial elemental content, particularly calcium[20,25]. The structure of other cellular organelles appears unaffected by light. The addition of EGTA or the ionophore A23187 to the external bathing medium significantly enhances these morphological transformations in response to light and to a much smaller extent produces dark conversions of lipochondria to the lamellar form. Lowering the temperature greatly reduces the number of morphological conversions during illumination.

Threshold light intensities of a number of photoreceptive systems

Preparation	Threshold intensity (W/cm^2)	References
Human absolute threshold for vision	2.0×10^{-14}	Wald, Brown and Gibbons[27]
Pseudemys scripta, turtle cone	1.2×10^{-11}	Baylor and Hodgkin[35]
Pecten irradians, scallop ocular photoreceptors		
Proximal depolarizing	8.0×10^{-10}	McReynolds and Gorman[28]
Distal hyperpolarizing	4.0×10^{-7}	
Rana temporaria, frog pineal nerve	1.0×10^{-9}	Dodt and Heerd[30]
Limulus polyphemus, horseshoe crab ommatidium	1.5×10^{-9}	Fuortes and Hodgkin[36]
Spisula solidissima, surf clam pallial nerve	6.0×10^{-9}	Kennedy[31]
Aplysia californica, sea hare		
Optic nerve	1.0×10^{-8}	Waser[26]
Abdominal ganglion R_2	4.3×10^{-4}	Brown, personal communication
Ventral photoresponsive neuron	4.1×10^{-7}	Andresen[37]
Passer domesticus, sparrow extraretinal brain, photoregulation of testis growth	1.5×10^{-8}	McMillan et al.[38]
Salpa democratica, pelagic tunicate ocular photoreceptor	6.4×10^{-7}	McReynolds and Gorman[29]
Salmo gairdnerii irideus, trout pineal photoreceptor	1.6×10^{-6}	Tabata, Tamura and Niwa[39]
Procambarus clarkii, crayfish caudal photoreceptor	6.5×10^{-6}	Larimer[40]

Absolute sensitivity of Aplysia extraretinal photoreceptors

Although very similiar in cellular morphology, VPN and R_2 have dramatically different degrees of light sensitivity. Threshold slowing of spontaneous spiking in VPN requires only about 10^{12} photons/cm^2 and is thus comparable to the threshold for *Aplysia* ocular responses[8,26]. Threshold hyperpolarization in R_2, however, requires more than 10^{15} photons/cm^2 (Krauhs et al.)[11]. In addition VPN responds in a graded fashion to stimuli graded in intensity over 3 orders of magnitude, while the range of intensities between threshold and saturation responses in R_2 is generally a 10-fold change or less. Thus VPN has both greater sensitivity and range than R_2.

A detailed comparision of the neuronal structure and ultrastructure of R_2, VPN and 2 non-photoresponsive, pigmented neurons failed to reveal a distinguishing morphological feature which could be associated with the degree of light sensitivity[11]. All 4 neurons contain morphologically similar lipochondria in similar numbers related to cell volume. Illumination produces similar conversions of lipochondria toward the lamellar form in all 4 neurons. Thus light sensitivity appears to require more than the presence of lipochondria and may require some further factor(s) for effective linking between chromophore light absorption and membrane events.

The absolute threshold for vision in humans has been estimated to be approximately 10^{-14} W/cm^2 (Wald et al.)[27]. Certainly the ocular threshold in *Aplysia* is much higher, requiring intensities of 10^{-8} W/cm^2 (Waser)[26]. VPN, an extraretinal photoreceptor has a threshold comparable to the animal's ocular threshold (table). On an absolute scale VPN is as sensitive as some retinal photoreceptors, *Pecten irradians* distal receptors[28] and *Salpa democratica* ocular photoreceptors[29] and less sensitive than some other extraretinal systems, frog pineal nerve[30] and clam pallial nerve[31]. The differences in absolute sensitivity of these various photoresponses reflect primarily the efficiency of photon capture by chromophore and, therefore, are related to the total amount of pigment present and the allignment of the pigment molecules with the respect to incoming light. However the transduction event is graded in nature and the basic mechanism is independent of the number of quanta activated.

Theory for the phototransduction mechanism

The experimental evidence indicates that calcium is responsible for triggering the effects at the plasma membrane measured as the photoresponse. A likely source of this calcium is the lipochondria which also contains the photopigment. Thus phototransduction would involve photon absorption by retinol in the lipochondria followed by release of calcium into the

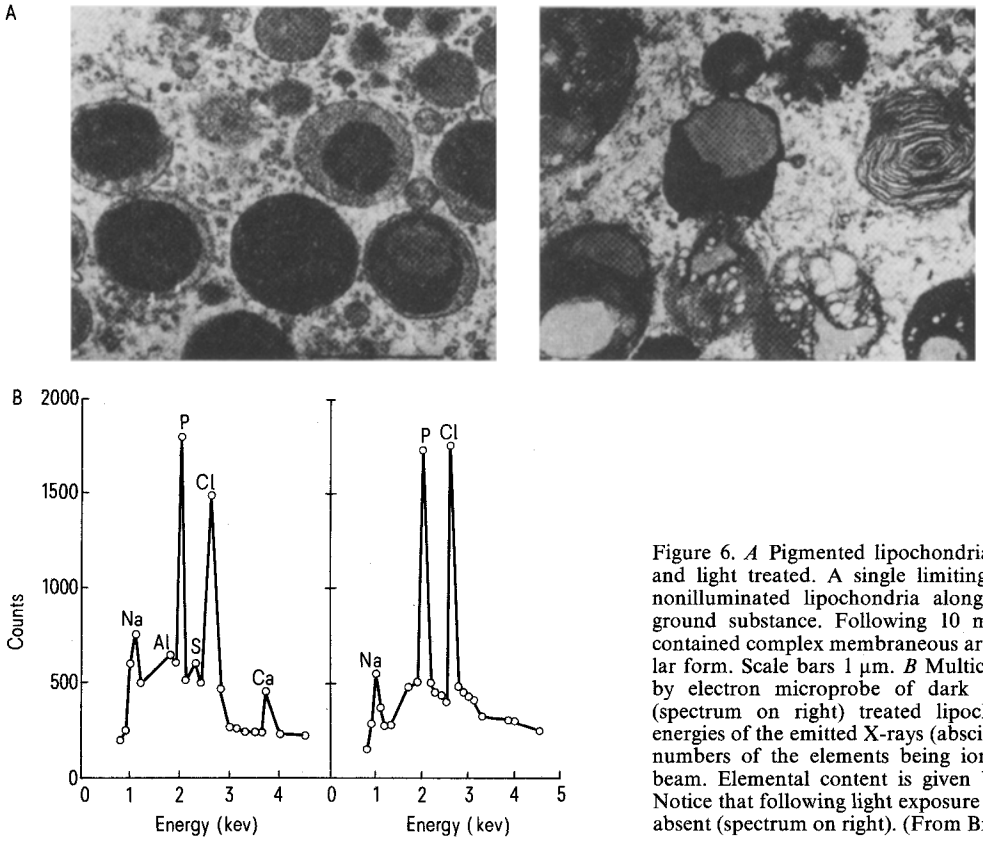

Figure 6. *A* Pigmented lipochondria from R_2 neurons, both dark and light treated. A single limiting membrane is evident in the nonilluminated lipochondria along with a moderate density of ground substance. Following 10 min illumination, lipochondria contained complex membraneous arrays characteristic of the lamellar form. Scale bars 1 μm. *B* Multichannel X-ray spectra obtained by electron microprobe of dark (spectrum on left) and light (spectrum on right) treated lipochondria in R_2 neurons. The energies of the emitted X-rays (abscissa) are functions of the atomic numbers of the elements being ionized by the incident electron beam. Elemental content is given by the area under each peak. Notice that following light exposure for 10 min, the calcium peak is absent (spectrum on right). (From Brown et al., 1975.)[25]

cytoplasm (fig. 7). The calcium would then diffuse to the plasma membrane and activate the potassium conductance. The activation process would be virtually instantaneous given the time scale of the light response since it occurs within 10-20 msec[32,33]. Thus the diffusion is the rate-determining process and it was reasonable to interpret the kinetics as well as the steady state light responses with such a model[34]. The model involved 3 processes, diffusion of calcium released from the lipochondria by light plus binding to cytoplasmic ligands, calcium-binding reactions at plasma membrane sites controlling potassium conductance and active uptake by calcium pumps presumably in the membrane and cytoplasmic organelles such as the lipochondria (fig. 7). The 3 essential compartments of the model correspond to cellular components: the lipochondria, the cytoplasm and the plasma membrane. Lack of space prevents discussion of the details which are available in the paper by Andresen et al.[34]. Suffice it to say that the model adequately predicts the experimental response waveforms (fig. 7), the effects of temperature and the stimulus-response relationship. In addition, model-based calculations of the cytoplasmic diffusion coefficient and transport rate of calcium efflux yielded values comparable to measurements reported in the literature. Thus the diffusion process dominates the transient and steady state characteristics of the measured membrane response.

The mechanistic parallels between highly differentiated photoreceptors such as the vertebrate rod and simple extraretinal photoreceptors such as VPN and R_2 suggest that the basic phototransduction scheme may be fundamentally similar and perhaps uniquely efficient. The internal transmitter feature of the transduction scheme potentially confers a method of linking and/or coordinating a variety of output responses. Thus the sequence of light absorption, chromophore transformation (isomerization) and transmitter release form the basis of phototransduction. Generation of internal transmitter then provides the linkage to the output mechanism. In the case of calcium, the internal transmitter could alter membrane transport processes. The transmitter could also be involved in hormone

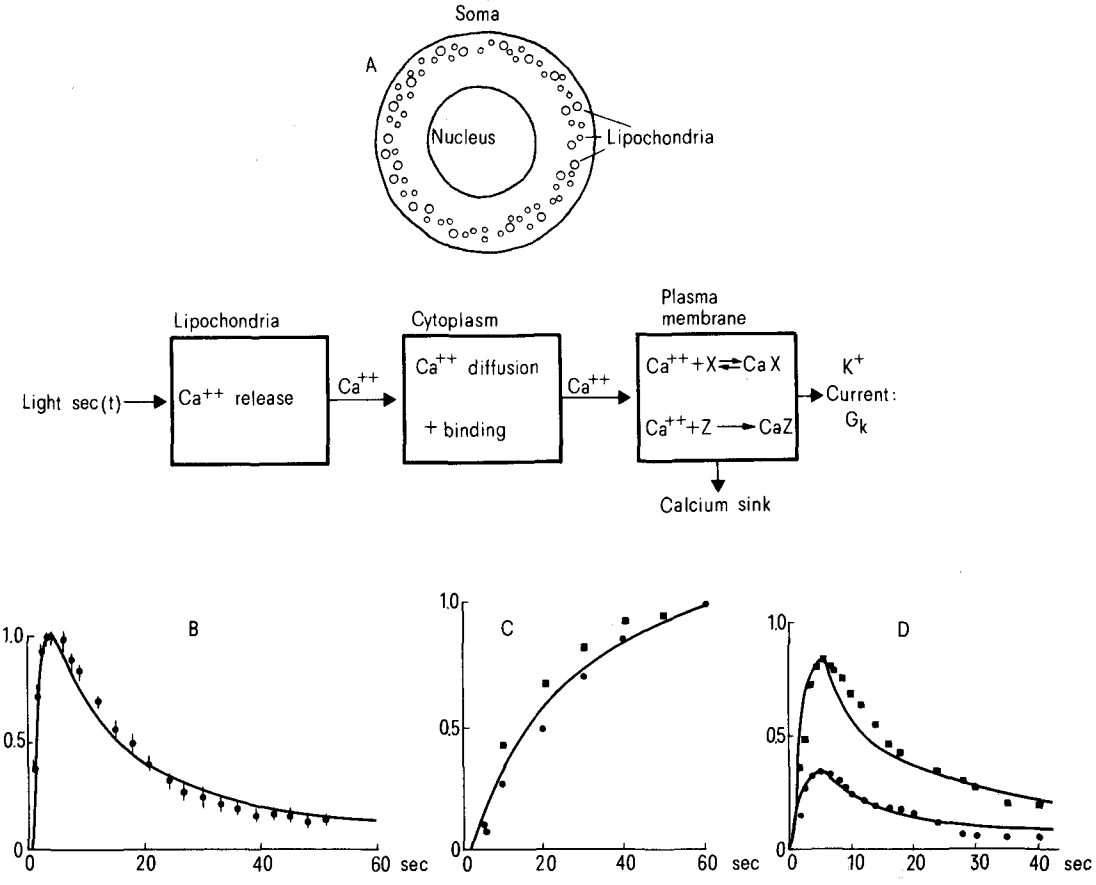

Figure 7. The diffusion-chemical reaction model. The neuron soma is spherical in shape and the nuclear radius is generally one-half the somal radius (A). The photopigment, probably a retinol derivative[22], and calcium are located in the lipochondria. The lipochondria are located in a shell extending from the plasma membrane inward toward the nucleus and are represented as small spheres in the diagram. The basic stages of the phototransduction process are indicated in the block diagram. Model details and equations are discussed in Andresen et al.[34]. The model successfully predicts response waveforms (solid lines, B–D) to a variety of stimuli including impulses of light (B, filled circles are the mean of nine light-induced current responses to 100-msec flashes ±SD), step illuminations (C), and impulses of light with different background illuminations (D). For details see Andresen et al.[34]. (Adapted from Andresen et al., 1979.)[34]

release or modulation of metabolic or enzymatic processes. In addition, with an effector such as calcium, phototransduction need not necessarily be confined to neuronal cells. In the *Aplysia* system as well as in vertebrate rods, calcium seems to be closely involved with the chromophore photon absorption-activation step. The presence of a common step in such phylogenetically distant cases may suggest that this process is uniquely suited for converting photon absorption to an output signal.

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