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Simulation of the AII amacrine cell of mammalian retina: Functional consequences of electrical coupling and regenerative membrane properties

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Abstract

The AII amacrine cell of mammalian retina collects signals from several hundred rods and is hypothesized to transmit quantal "single-photon" signals at scotopic (starlight) intensities. One problem for this theory is that the quantal signal from one rod when summed with noise from neighboring rods would be lost if some mechanism did not exist for removing the noise. Several features of the AII might together accomplish such a noise removal operation: The AII is interconnected into a syncytial network by gap junctions, suggesting a noise-averaging function, and a quantal signal from one rod appears in five AII cells due to anatomical divergence. Furthermore, the AII contains voltage-gated Na+ and K+ channels and fires slow action potentials *in vitro,* suggesting that it could selectively amplify quantal photon signals embedded in uncorrelated noise. To test this hypothesis, we simulated a square array of AII somas (Rm = 25,000 Ohm-cm2) interconnected by gap junctions using a compartmental model. Simulated noisy inputs to the AII produced noise (3.5 mV) uncorrelated between adjacent cells, and a gap junction conductance of 200 pS reduced the noise by a factor of 2.5, consistent with theory. Voltage-gated Na+ and K+ channels (Na+: 4 nS, K+: 0.4 nS) produced slow action potentials similar to those found *in vitro* in the presence of noise. For a narrow range of Na+ and coupling conductance, quantal photon events (~5-10 mV) were amplified nonlinearly by subthreshold regenerative events in the presence of noise. A lower coupling conductance produced spurious action potentials, and a greater conductance reduced amplification. Since the presence of noise in the weakly coupled circuit readily initiates action potentials that tend to spread throughout the AII network, we speculate that this tendency might be controlled in a negative feedback loop by up-modulating coupling or other synaptic conductances in response to spiking activity.

Keywords: Neural network, Synaptic noise, Computer simulation, Gap junction

Introduction

The retina of mammals contains a sequence of rod-driven neurons (Famiglietti & Kolb, 1975) collectively named the "rod bipolar pathway" (Smith et al., 1986) that carries the rod signal at scotopic intensities (i.e. starlight to twilight). In starlight, a rod absorbs only one photon every few minutes, transducing it into a signal less than 1 mV in amplitude (monkey: Baylor et al., 1984; Schnapf et al., 1994), so the rod bipolar pathway therefore must collect such tiny "single-photon" signals (Freed et al., 1987). Yet such signals have never been directly observed in the mammalian retina in neurons other than the rod. However, at low scotopic intensities single photons can be detected by analysis of spike recordings from cat ganglion cells (Barlow et al., 1971; Mastronarde, 1983), in the ERG (Robson et al., 1994), and also psychophysically (Sakitt, 1972; but see Makous, 1990), so the rod bipolar pathway is hypothesized to preserve their quantal identity (Smith et al., 1986). Such a quantal signal would represent the smallest visual sensation observable by the brain, so how the retina might amplify and filter it is the subject of considerable interest.

The third neuron in the rod bipolar pathway is the AII amacrine, which in the cat retina collects signals originating in about 500 rods (Fig. 1; Sterling et al., 1988). Since the rod's single-photon signal is noisy (S/N ratio = 5; Baylor et al., 1984), such convergence of the rod signal presents a problem for the neural circuitry. The problem is that the rod noise continues even when no photon signals are transduced, which implies that the signal in the AII from one photon would be lost in the continuous noise from 500 rods were special care not taken to preserve it.

Baylor et al. (1984) first pointed out that this problem would exist when as few as ten rods converge on the second-order neuron (the rod bipolar cell), because noise sums with the square

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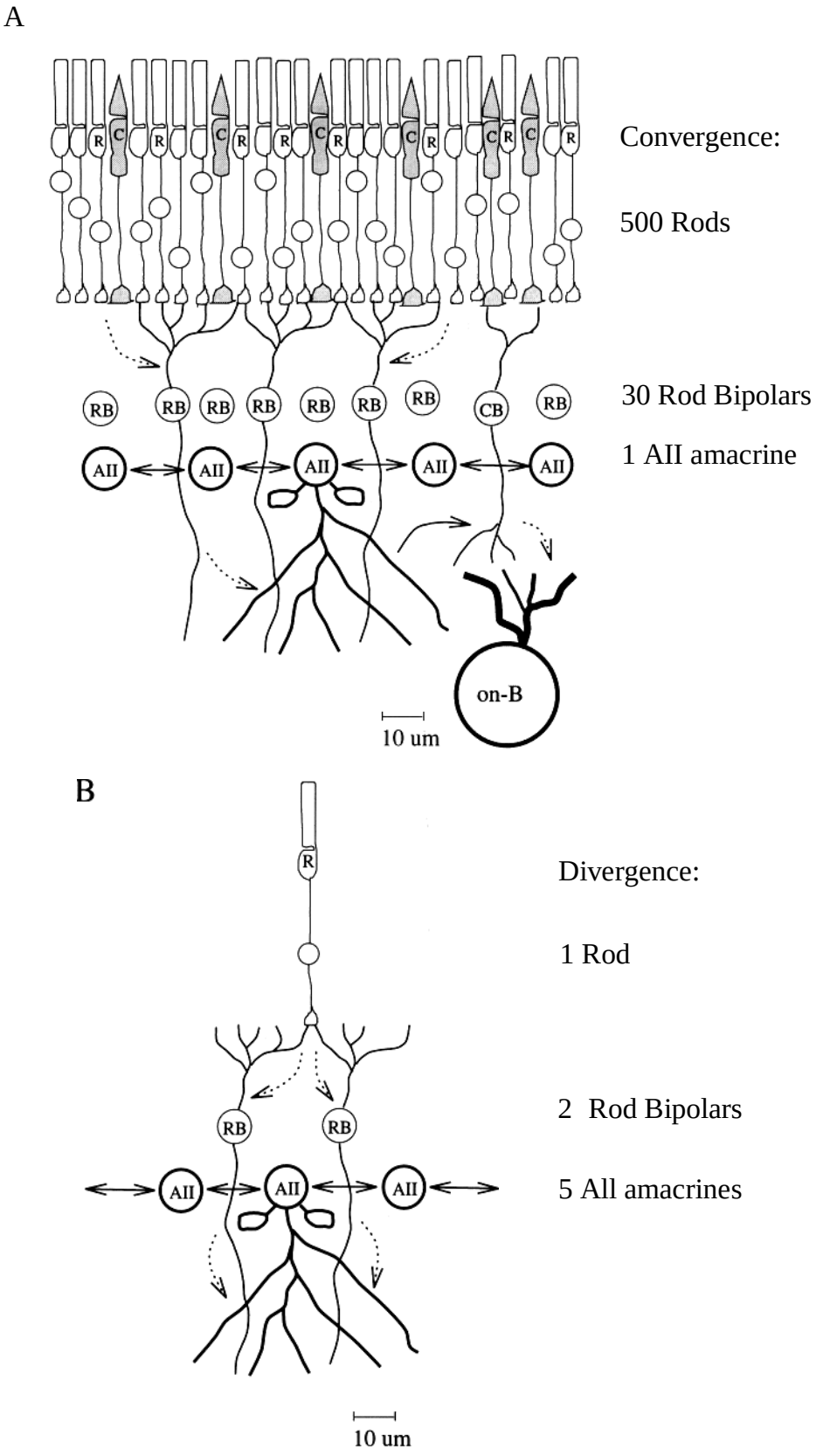


Fig. 1. A: Convergence in the rod bipolar pathway from rods to the AII amacrine. In cat, about 500 rods converge through chemical synapses (dashed arrows) to 30 rod bipolars to one AII. The AII is connected through lateral electrical synapses (gap junctions, solid arrows) into a network. From the AII, the rod signal is transmitted through gap junctions to the b1 cone bipolar and thence to ganglion cells. B: Divergence in the rod bipolar pathway. One rod diverges to two rod bipolars which contact up to five AII amacrines.

root of the number of (independent) noise sources. Baylor et al. suggested that a thresholding operation could remove the baseline noise, and if this were performed at the chemical synapse between the rod and rod bipolar, the convergence of 15 rods to one rod bipolar found in the cat retina could be tolerated without losing the quantal nature of individual photon signals.

The AII amacrine has a similar problem because it receives, in a second stage of convergence, signals from about 30 rod bipolars (Sterling et al., 1988). If the AII merely summed signals from all 30 rod bipolars, a quantal signal would again be overwhelmed because the noise would increase by a factor of sqrt(30) or about 5. Thus, to understand how the pathway transmits quantal photon signals one might look for "thresholding devices," elements in the neural circuit that could nonlinearly amplify a signal to remove baseline noise.

The AII amacrine cell has a narrow dendritic field (<50 μm in cat *area centralis),* but is electrically coupled into a network by large gap junctions (Famiglietti & Kolb, 1975; Vardi & Sterling 1989; Vaney, 1991). The presence of electrical coupling seems to be a clue because it is known to reduce noise in a network (Lamb & Simon, 1976; Tessier-Lavigne & Attwell, 1988). However, coupling is also known to reduce the S/N ratio of a signal injected into one cell in such a network, because although the noise is reduced, the signal is reduced by a larger factor (Lamb & Simon, 1976).

Thus, the AII's lateral coupling would appear to worsen the problem, except for the presence of two other elements in the circuit. First, the signal from one rod diverges through the rod bipolar pathway to about five AIIs (Fig. I; Sterling et al., 1988). According to the theory of noise reduction by coupling (Lamb & Simon, 1976), if electrical coupling in the AII were to spread its signal by an amount equivalent to the divergence of a single photon (i.e. a space constant of about 1-2 cells), the coupling would in fact reduce noise while maintaining the photon signal. Second, patch recordings reveal that the AII contains voltage-gated Na+ and K+ channels and under some circumstances *in vitro* can initiate action potentials (rat: Boos et al., 1993). Such channels might be responsible for the pronounced transient recorded in the AII response to a light flash in the perfused eyecup preparation (cat: Nelson, 1982; rabbit: Dacheux & Raviola, 1986). Therefore, it seems possible that the regenerative properties of the Na+ channel might be the site for nonlinear amplification in the AII which could be the "thresholding" device discussed above. Indeed, at intensities where the AII light response has been measured to disappear into its noise, a "threshold nonlinearity" shortens its response risetime (Nelson, 1982).

From these observations, therefore, we hypothesized that the AII circuit is designed to remove baseline noise from a stream of embedded quantal events. To evaluate this hypothesis, we constructed a compartmental model of the AII array that contained a simplified version of the circuit elements outlined above. The point of the study was to verify whether a quantal event could be selectively amplified by the circuit, and if so, to explore how the circuit functioned under various conditions and suggest a reasonable combination of coupling and membrane channel parameters that could be tested empirically.

Methods

We simulated the network of AII cells as an array of spherical isopotential somas (7 wm diameter, Sterling et al., 1988) with the NeuronC simulation language (Fig. 2; Smith, 1992). Each AII soma was represented by one compartment that contained membrane resistance, capacitance, a synaptic conductance, and a voltage-gated membrane channel. Membrane resistance *(Rm* = 25,000 Ohm-cm2) was chosen to limit the membrane time constant to 25 ms (see Boos et al., 1993; Nelson, 1982). Gap junctions were simulated as ohmic conductances, and were tested in the range of 100-2000 pS.

Synaptic inputs and noise

Synaptic inputs to an AII were simulated as a presynaptic terminal containing a neurotransmitter release function of voltage that modulated a depolarizing synaptic conductance *(Erev -10* mV, 120 pS) in the AII membrane (see Table 1). Each AII received input from only one terminal. The AII resting potential was set by varying its tonic synaptic input through voltage clamp of the presynaptic terminals to a level between -50 and -60 mV. Responses normally peaked negative to -40 mV, avoiding severe saturation in most cases (synaptic *Erev = -10* mV, leak *Erev* = -70 mV). Neurotransmitter release was modulated by noise consisting of Poisson-related vesicle events (2-ms duration). Vesicle release rate for the Poisson function was set by the simulator proportionate to instantaneous release divided by vesicle event size (set manually as parameter; 1 = half-saturating), so the level of synaptic noise relative to the signal (i.e. mean vesicle release rate) was set by adjusting vesicle event amplitude. For most simulation runs vesicle release rate was about 180/s.

Although the pattern of noise was different from one AII to the next, simulation runs that defined identical stimuli produced the identical pattern of noise from one run to the next. One risk of this method was the generation of non-representative parameter dependencies, which might be corrected by averaging data from several simulation runs with different noise waveshapes. However, we preferred the analysis of individual noise waveshapes to develop intuition about how the neural circuit's biophysical properties process signals, especially since nonlinearities were involved. In all cases, where noise was superimposed with the signal we ran several noise waveshapes to verify

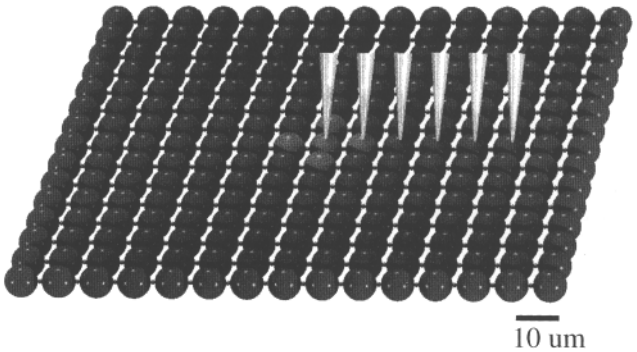


Fig. 2. Model of AII network (15 x 15). AIIs were simulated as single compartments (dark gray spheres) and were coupled into a square array with gap junctions (small spheres between large ones). The five most central AIIs (light gray spheres) were presented with stimulus. Responses were recorded from six AIIs (spaced at 8-μm intervals) along a radius starting from the central cell, and the responses thus recorded represented the receptive field of the central cell. Model also included presynaptic terminals and noisy synapses (not shown; see Methods).

Table 1. *Standard parameter values for simulation*

AII	
Array dimensions	15 x 15
Soma	7 μm diameter
Rm	25,000 Ohm-cm2, *Erev -70* mV
Cm	*1* μf/cm2
Na+ conductance	*4* nS, *Erev = +40* mV
K+ conductance	0.4 nS, E*rev* = -80 mV
Gap junctions	200 pS
Synaptic input	
Synaptic gain	3 mV/e-fold increase in conductance (G).
Synaptic threshold	*45* mV produces *2.5%* of maximum G
Synaptic conductance	*1.2* nS maximum
Reversal potential	*Erev = -10* mV
Synaptic events	*2* ms duration
Resting event rate	180/s
Random function	Poisson
Stimulus	
Rise time	100 ms
Fall time	100 ms
Amplitude	*5-10* mV in central All

the conclusions reported here; thus, waveshapes in Figs. 4-8 are not "average" but are "representative" waveshapes that illustrate a point. The noise pattern changed whenever either (1) the simulation's "random seed" or number of synapses was changed, or (2) the stimulus amplitude changed, e.g. a presynaptic depolarization increased noise (see Fig. 8).

Stimuli and voltage-gated channels

Quantal photon events were simulated by depolarizing either one or five presynaptic terminals with a "photon" event (3-5 mV, 100-ms rise time, 100-ms fall time). The event was transmitted to the AII through an exponential synaptic transfer function (3 mV/e-fold change) that slightly accentuated the event's peak (see Fig. 6B). Voltage-gated Na+ and K+ channels were simulated as standard voltage-gated channels in the manner of Hodgkin and Huxley (1952), except that the activation/inactivation rates were modified and the K+ conductance in a compartment was reduced (Na+/K+ ratio = 10). The simulated Na+ and K+ channels were run at 22 deg (Boos et al., 1993) by multiplying their rate constants by a factor of 5.6, assuming a Q10 of 3 (Hodgkin & Huxley, 1952). In addition, Na+ inactivation (αh and βh) rate constants were divided by a factor of 3.5, and K+ activation (αn and βn) was divided by a factor of 5, producing prolonged action potentials that approximated those recorded by Boos et al., 1993. In preliminary simulations, AII somas on the array edge produced spurious action potentials because their input resistance was artifactually higher than more central AIIs. We reduced this dynamic "edge effect" by removing Na+ and K+ channels from the AIIs in edge rows and columns in all simulations and increasing the initial 12 x 12 array to 15 x 15. Intracellular voltages and synaptic and membrane channel state variables could be plotted from any component of the circuit during the simulation.

Results

The AII array was simulated as a square grid (15 x 15) interconnected by gap junctions (see Lamb & Simon, 1976). An AII was connected with its four closest neighbors except when it was at the array's edge (see Fig. 2). In an initial series of simulations, we tested signal spread through the gap junctions. With only the central AII stimulated, gap junctions of 400-1000 pS produced a space constant for the AII network of about 1 cell (Fig. 3A), the approximate radius of divergence of a single-photon signal (1 rod -> 5 AIIs). To test the advantage of gap-junction coupling in the presence of a correlated input signal (see Lamb & Simon, 1976; Tessier-Lavigne & Attwell, 1988), a "quantal photon event" was supplied to the central five AIIs (Fig. 3B) and the amplitude adjusted to be about 5-10 mV when coupled (Fig. 3D). When only one AII had received the signal, coupling sharply reduced it (Fig. 3C), but when the five central AIIs received the signal, coupling of 200 pS reduced it by only 25% (Fig. 3D), consistent with theory (Lamb & Simon, 1976; Tessier-Lavigne & Attwell, 1988).

To test the noise-reducing action of the gap junctions, synaptic noise in the AII was set without gap junctions to be 3.5 mV (S.D.) (Fig. 4A). A functional conductance of 200 pS reduced noise by a factor of 2.5, and 1000 pS reduced noise by a factor of 5 (Figs. 4B and 4C), consistent with theory (Lamb & Simon, 1976). As expected, with only one AII stimulated these noise reduction factors were less than the corresponding signal reduction factors so the AII's S/N ratio worsened (see Tessier-Lavigne & Attwell, 1988). However, in the presence of "rod-AII divergence" (1:5) a coupling of 200 pS increased S/N ratio by a factor of almost 2, demonstrating the benefit of rod-AII divergence in the presence of gap-junction coupling.

Na+ and K+ channels (Na+: 4 nS; K+: 0.4 nS peak conductance) were then added to the AIIs. Without the quantal event or coupling, synaptic noise tended to evoke spontaneous action potentials (Fig. 5). Na+ inactivation and K+ activation time constants were adjusted to give "slow" regenerative action potentials similar in duration (~ 15 ms width at half-height) to those found *in vitro* (Boos et al., 1993; Nelson, 1982; Dacheux & Raviola, 1986).

In the presence of both coupling and Na+ channels, different behavior occurred with different combinations of coupling or Na+ channel conductances. A large coupling conductance (> 1 nS) tended to inhibit spontaneous action potentials and reduce the amplitude of signal-driven subthreshold events (see Hodgkin & Huxley, 1952). Intermediate values of coupling produced "partial" action potentials restricted to the five stimulated AIIs (Fig. 6A) or "full" action potentials initiated by spurious noise (Fig. 6C). When Na+ channel conductance was increased (to 6 nS, in an attempt to boost signal-driven action potential amplitude), every AII fired in the network synchronously (not shown).

Under some conditions, voltage-gated Na+ and K+ channels boosted the response of the stimulated AIIs to the slowly rising quantal photon event (Fig. 6). The effect was dependent on four factors: (1) an intermediate amount of gap-junction coupling (standard value 200 pS), (2) a depolarizing quantal event of sufficient amplitude (5-10 mV) applied to an adjacent group of AIIs, (3) active Na+ and K+ membrane channels with appropriate voltage and temporal activation properties, and (4) the presence of noise (Figs. 6A, 6B, and 7A). A lower coupling conductance gave greater "signal boosting" but allowed noise to initiate occasional action potentials (Fig. 6C). Increasing the coupling conductance to 400 pS shunted the signal laterally and reduced amplification by Na+ channels (Fig. 7B). If instead

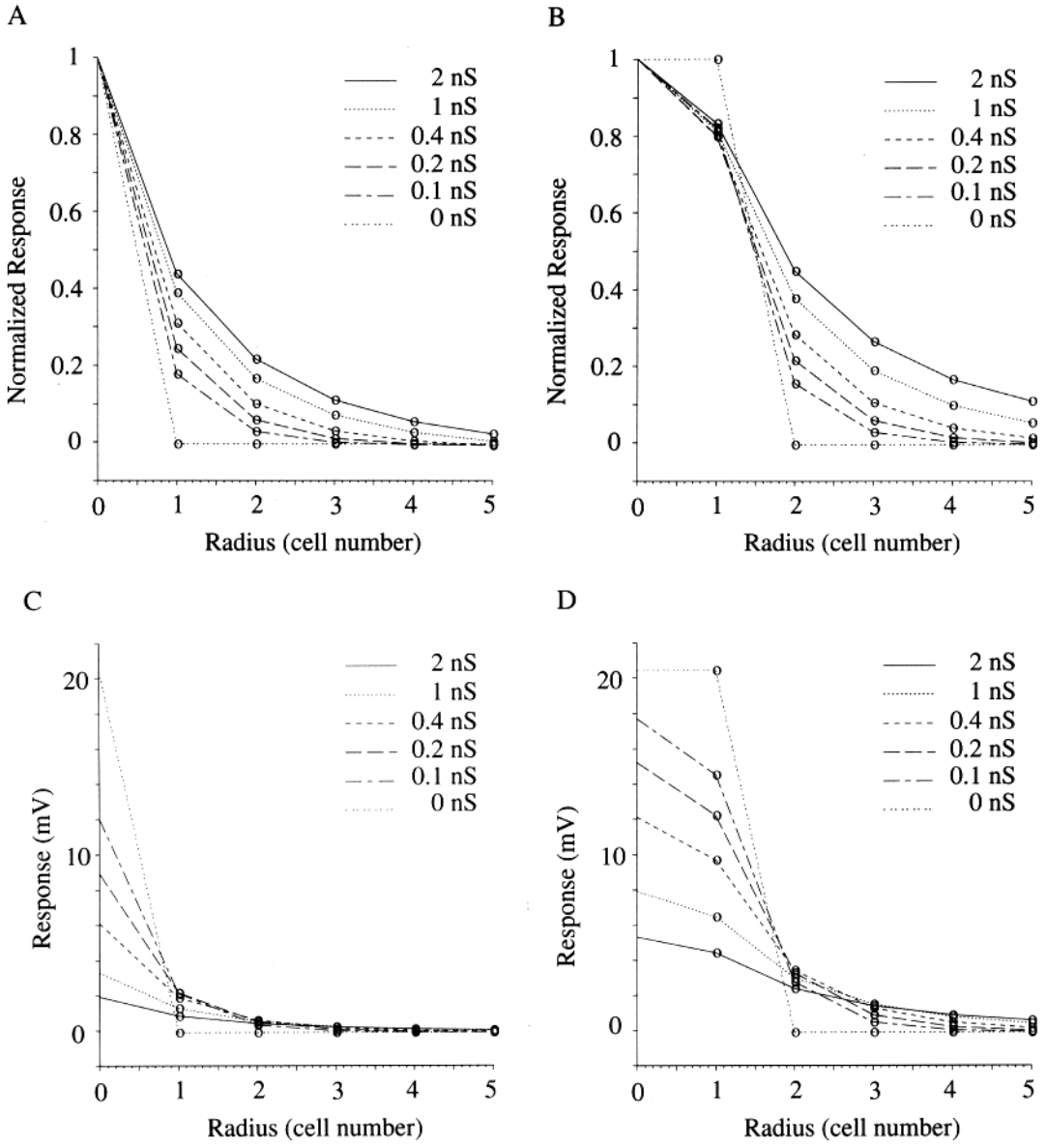


Fig. 3. Responses taken from six AII cells in network along a radial line to a central stimulus plotted to approximate receptive fields. A: Normalized receptive fields of AII network to point stimulus at central cell with different amounts of electrical coupling. Increased coupling conductance widens receptive field, consistent with theory. Note that response of network without coupling (0 nS) does not imply a correct receptive-field profile since model did not include dendritic anatomy. B: Normalized responses to same stimulus as in A except presented to five most central cells, simulating divergence from one rod to five AIIs. C: Absolute response amplitudes with stimulus given to one cell. In addition to widening receptive field, coupling reduces the height of response (proportionate to square root of coupling conductance). D: Absolute responses when stimulus was presented to five most central cells. Moderate coupling conductance widens receptive field (i.e. spatial extent of cells in network that respond to stimulus) but does not decrease amplitude much because stimulus is matched to receptive-field diameter.

one AII was stimulated (in the presence of 200 pS coupling), the signal was shunted in a similar way (Fig. 7C).

When the "quantal event" stimulus was given an instantaneous rise time, the AII network responded with a subthreshold event (i.e. voltage transient) near stimulus onset but delayed by about 25 ms. The effect was dependent on the fast stimulus rise time and was most pronounced when a noise peak coincided with the underlying Na+ activation (Fig. 8).

Discussion

The results suggest that the AII circuit can function as hypothesized to selectively amplify a quantal single-photon signal mixed with noise. The simulated AII network sums multiple quantal signals arriving simultaneously in adjacent AII cells, averaging out uncorrelated noise and nonlinearly amplifying the common signal. Since gap junctions are widely distributed in the retina

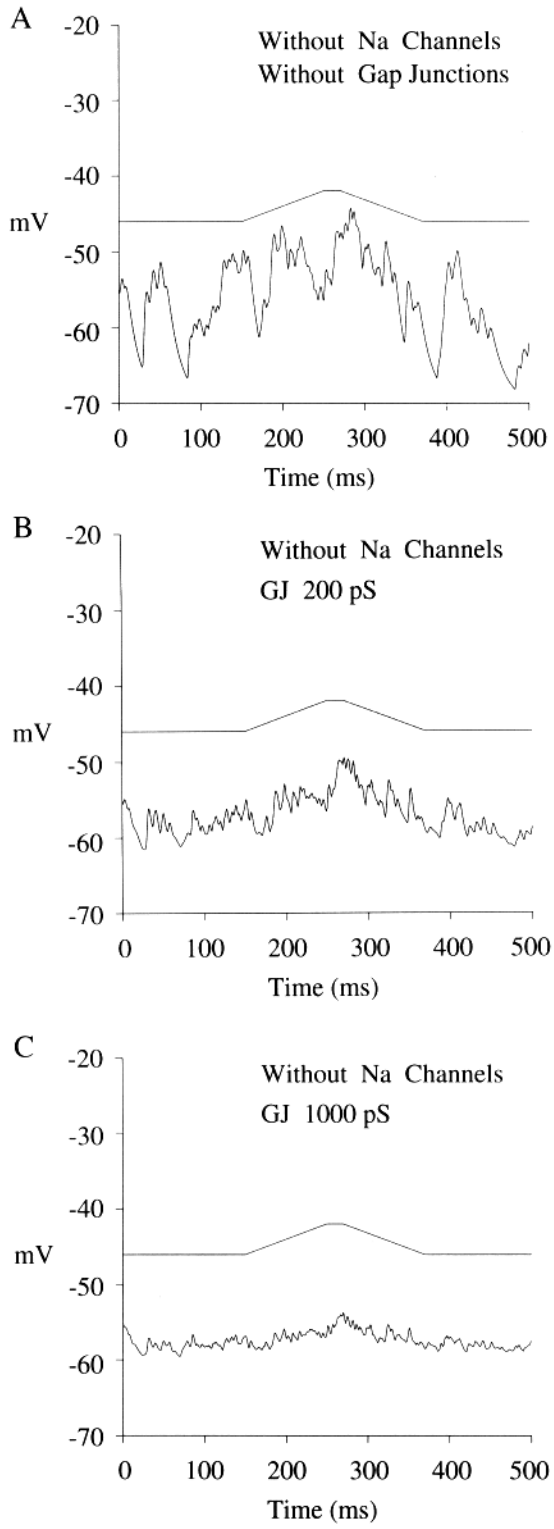


Fig. 4. A: Voltage record from central AII in network without voltage-gated Na+ membrane channels or gap junctions. Top trace: "Single photon" stimulus recorded in presynaptic terminal, 100-ms rise time with 20-ms peak and 100-ms fall time, applied to five central AIIs in network. Bottom trace: response to photon stimulus (about 10 mV) is lost in noise (3.5-mV standard deviation). B: Same model except gap-junction conductance 200 pS; response to stimulus is now obvious. Averaging by gap junctions reduces noise more than signal. C: With greater coupling conductance, response to signal is diminished along with amplitude of noise.

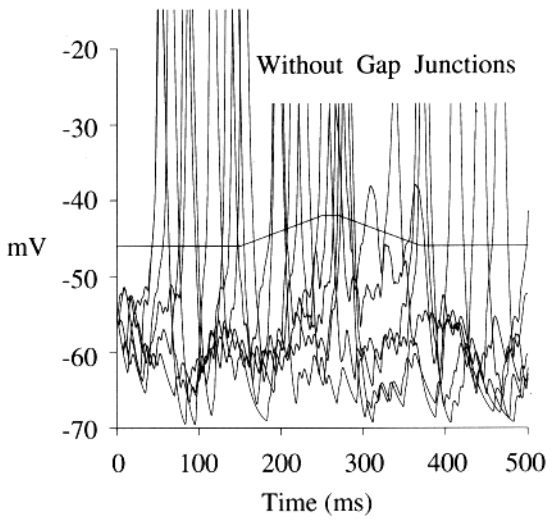


Fig. 5. Superimposed voltage records from six AIIs taken in radial line from center of array (see Fig. 2), with voltage-gated Na+ channels (4 nS) but without gap junctions. AIIs generate continuous asynchronous action potentials.

and other neural tissues and voltage-sensitive channel properties are also widespread, the operation of the circuit described here could represent a general mechanism in the brain for selectively amplifying a signal in the presence of noise.

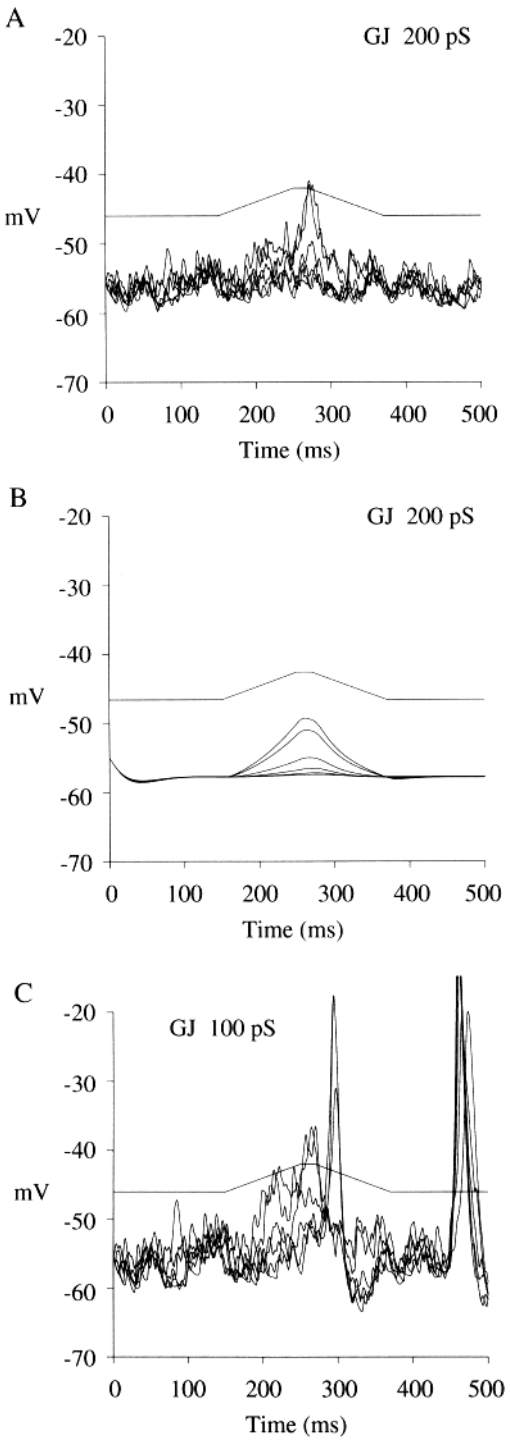
A slightly different hypothesis was proposed by Boos et al. *(1993)* for the AII's function. Their data showed the presence of multiple superimposed action potentials which suggested that Na+ channels could reside in the dendritic membrane far enough electrotonically from the soma to provide independent sites for action potential initiation. They suggested that Na+ channels could therefore perform a "local booster" function. Since AII morphology varies across the retina, this suggestion might appropriately apply to the AII of peripheral retina that has relatively long but fine dendrites in sublamina *B* of the inner plexiform layer (Vaney et al., *1991).*

In a preliminary simulation of a central AII derived from measurements of a series of electron micrographs (see Sterling et al., *1988),* we have found that an AII near 1-deg eccentricity is electrotonically compact, all branches being well within one space constant (Vardi and Smith, unpublished manuscript). Although synaptic input in some cases can reduce the space constant along a dendrite (Bernander et al., *1991),* the AIIs synaptic inputs from rod bipolar cells sit on the robust dendritic tree that extends to sublamina *B* (Sterling et al., *1988),* which implies that their effect would not be much reduced by synaptic input of any source. Gap junctions are either located on the AII's soma or on dendritic branches in sublamina *B.* This suggests that such a smaller central AII, with dendrites not longer than *30* μm, would not generate separate action potentials originating in its dendrites. Therefore the AII is simplified here to one electrical compartment. Other factors in the circuit, e.g. gap junctions between the AII and On bipolars (Kolb & Famiglietti, *1974;* Sterling et al., *1988),* might affect the results but were not included in the model for the sake of simplicity, because their effect would presumably mimic coupling between AIIs and loading effects already parametrized into the model.

Correlation of noise

The increase in S/N ratio for a quantal photon signal depended partly on averaging of uncorrelated noise between synaptic inputs to an AII cell and between neighboring AII cells. One concern is the degree of correlation of noise inputs. Since the signal amplification mechanism described here relies on discrimination by amplitude, noise correlated between AIIs could prevent the AII circuit from discriminating the single-photon signal if the noise amplitude (2 * S.D.) was sufficient to mask the signal. Correlated noise would be immune to averaging by gap junctions, depending on how closely matched the space constant of correlation was to the space constant of network coupling.

Several putative noise sources of biological origin are presynaptic to the AII (rod transduction noise, synaptic noise from rod -> rod bipolar and rod bipolar -> AII, among others), and these sources would present partially correlated noise to adjacent AII cells (Fig. 1). For example, since a rod bipolar diverges to about four AII cells (Sterling et al., 1988), noise that originated in its synaptic inputs would be passed as a correlated signal to all four. If that rod bipolar also transmitted a single-photon signal, both noise and signal would arrive in a nearly identical pattern of AII cells (since a rod's signal is passed to about five AIIs; see Fig. 1), so noise that originated in the rod bipolar could not be reduced in relation to the single-photon signal by gap-junction coupling. Since many of the 30 rod bipolars that converge to an AII also diverge to the same set of neighboring AII cells (because one AII overlaps about four others, Vaney, 1985; Sterling et al., 1988), the noise correlated in this manner could be transmitted by a significant fraction of the rod bipolar inputs converging to the AII. Similarly, noise from one rod passes through two rod bipolars to five AIIs, so noise originating in most of the rods converging to the AII would also be highly correlated in adjacent AIIs. However, the component of rod bipolar noise which arrives in the AII array correlated in this manner is likely to be reduced by nonlinear processing at the rod bipolar (see Introduction; Baylor et al., 1984; Smith et al., 1986), so it may be a minor component. However, a rod bipolar contacts an AII with about five chemical synapses (Sterling et al., 1988) whose noise is presumably uncorrelated, since the exact timing of vesicle release and channel opening are random (Faber et al., 1992). Therefore, averaging within an AII and between neighboring AIIs through coupling would best serve to reduce this uncorrelated component originating in its numerous direct synaptic inputs.



Subthreshold spiking mode

Boos et al. (1993) report the AII produced "small spike-like" events in response to depolarizing current injection. The firing rate was sustained for relatively high current levels and dropped to zero below a modest depolarizing current. We did not attempt to simulate such a sustained firing pattern because the subthreshold mode of regeneration (i.e. a slow unitary spike-like event

Fig. 6. Superimposed voltage records from six AIIs taken in radial line as in Fig. 5. A: Standard parameters (see Table 1): central AII and its neighbor generate subthreshold events in response to single-photon stimulus, clearly projecting above the noise level. Effect of Na+ channels is evident in comparison with Fig. 4B. B: Control: same model with noise removed, showing amplitude of responses underlying noise. Compared to event in B, photon event in A is amplified by almost a factor of 2. Initial hyperpolarization in B is due to the fact that initial membrane potential (-55 mV, set manually correct for A) was depolarized from eventual *Erest.* Sodium-channel activation by noise in A and C is responsible for their relatively depolarized *Erest.* C: Same as A but with reduced gap-junction conductance. Since noise is exactly the same, response can be directly compared with A. Larger subthreshold event still apparent but full action potentials (e.g. at 450 ms) result from randomly correlated noise peaks in neighboring cells. A further decrease in coupling increases the frequency of such spurious events (see Fig. 5).

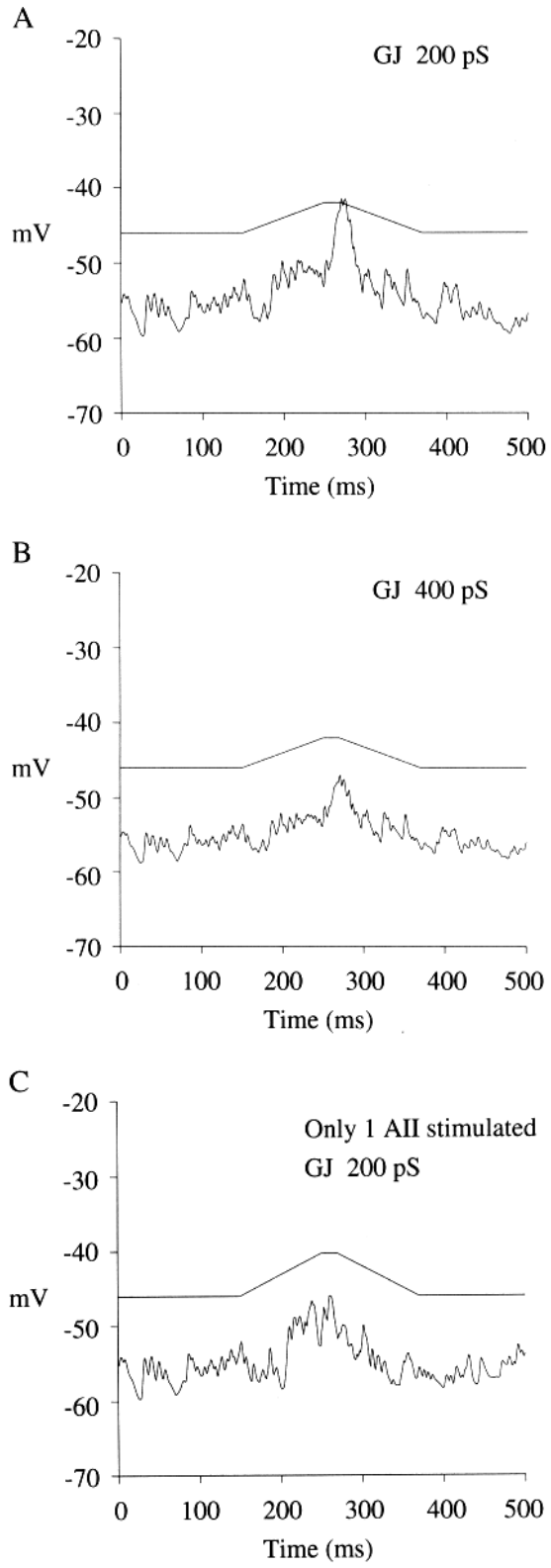


Fig. 7. Voltage record from central AII of model including voltage-gated Na+ channels and gap junctions. A: Trace from central cell in Fig. 6A; standard parameters, amplified single photon event clearly visible. Compare with Fig. 4. B: Stronger coupling reduces the amplification. C: Response with only one AII stimulated. Stimulus amplitude increased so response (when measured without noise) in central AII is same as in A. Amplification reduced because correlated signal is not present.

whose amplitude depended on the stimulus; see Hodgkin & Huxley, 1952) seemed more consistent with unitary spike events in the AII recorded from the whole retina (Nelson, 1982; Dacheux & Raviola, 1986) and the increase in rise time of AII responses when the stimulus was decreased to "threshold" (Nelson, 1982). Although the amplitude of the single-photon event in the AII is unknown, if the AII nonlinearly amplifies it based on voltage-gated membrane channels, their voltage-dependent properties must constrain the time course and amplitude of events that can be processed. Our choice of noise and quantal amplitude, therefore, was based on the behavior of the membrane channels in the simulation. Compared to synaptic transfer in other species (voltage gain of 10-100, see Ashmore & Falk, 1980), our assumption of a voltage gain of 10 (i.e. 0.5 mV ~ 5 mV) across two chemical synapses (from rod -> rod bipolar -> AII) seems plausible.

Although the Na+ and K+ channel parameters we chose surely do not precisely represent the *in vivo* channels (e.g. the parameters and types of channels involved are not fully known; Ca++ channels could be involved), the same issues must nevertheless exist. Our modifications of Hodgkin-Huxley parameters (reduction in K+ conductance relative to Na+; reduction of Na+ inactivation and K+ activation rate constants; see Methods) produced slow action potentials, but we did not attempt to find all combinations of channel parameters that might give similar results. The channels reported by Boos et al., 1993 appear to have relatively fast rates appropriate for mammalian cells at room temperature, and the K+ currents they measured were strong, so it is not clear what channel mechanisms generated the slow action potentials they found.

Synchronous firing

Strong coupling synchronized the network to the extent that if an action potential emerged, all cells fired together, obviously not a useful function for the retina. This was a concern only when the Na+ conductance was increased to the point where full action potentials occurred. As Boos *et al*. (1993) observed, the AII seems not to generate "full" action potentials so we reduced the Na+ channel conductance (e.g. to Na+: 4 nS/compartment) to limit regeneration to "subthreshold." In this case, stronger coupling (1 nS or above) inhibited local regenerative amplification of a quantal signal, though noise was greatly reduced. Weaker coupling (100-400 pS) in the presence of a large Na+ conductance also produced network-wide synchronous firing but in this case spikes in adjacent cells were sequentially delayed by the time constant derived from coupling conductance and membrane capacitance.

Nonlinear amplification

Combinations of weaker coupling (100-400 nS) and Na+ conductance (Na+: 4 nS) produced amplification of the quantal signal and noise peaks (Figs. 6 and 7). A higher Na+ conductance produced a greater amplification up to the point where the entire network produced full action potentials. The amplification could be damped by increasing coupling conductance; in fact, the two parameters had nearly opposite effects over a limited range. In the subthreshold mode, an essential condition for the simulated AII to amplify the photon signal was a quan-

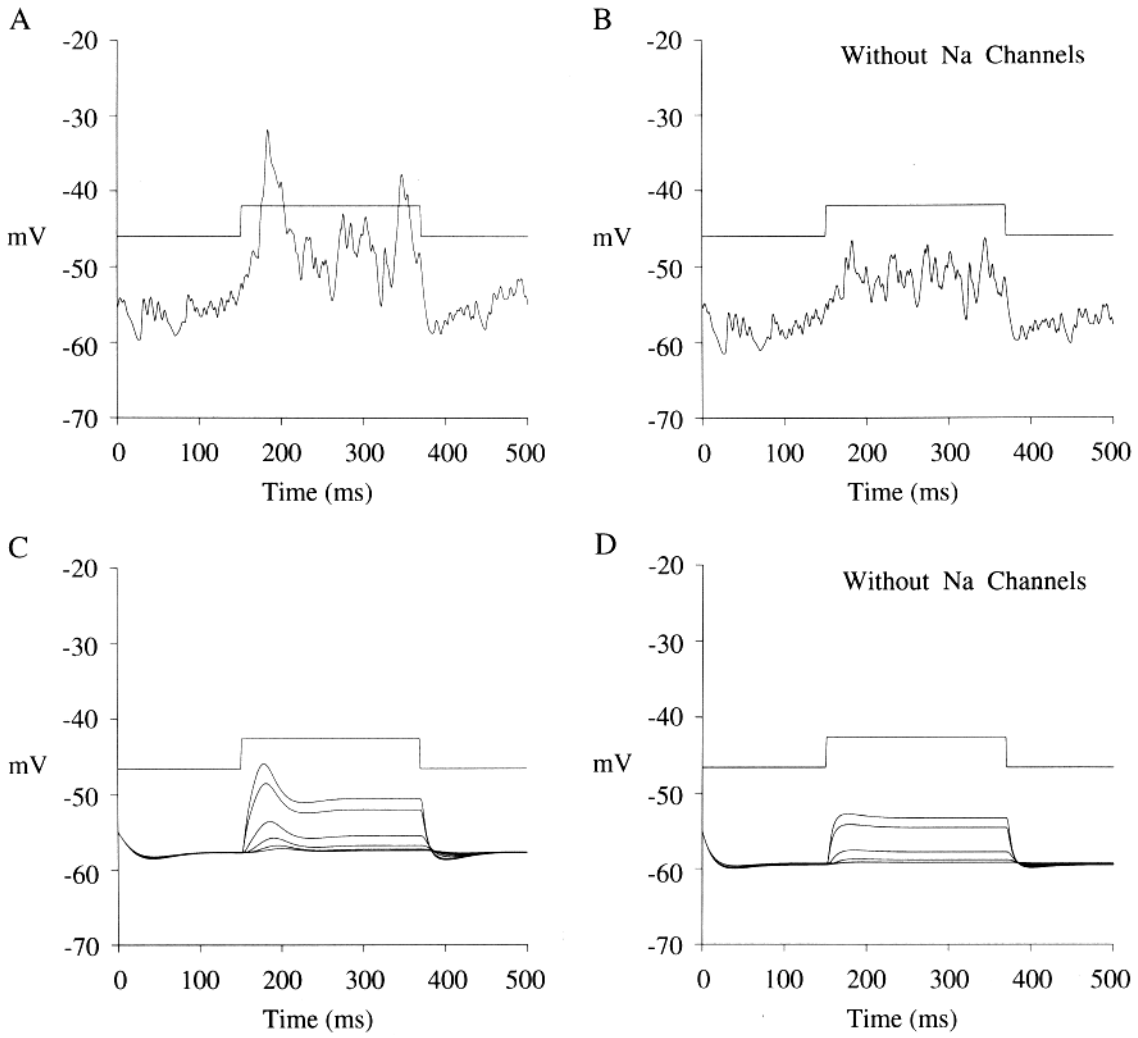


Fig. 8. Voltage record in central AII of standard model except with sharply rising stimulus event. A: Initial edge of stimulus produces clear transient in AII. Stimulus plateau produces increased amplitude noise because resulting depolarization activates Na+ channels and also because synaptic vesicle rate is increased. B: Same model without Na+ channels. Response is almost large enough to discriminate event. C: Same as A but response of six radial AIIs, and with noise removed. Na+ channels generate one subthreshold event in response to rising edge of stimulus. Comparison to Fig. 6B verifies that Na+ channels require fast edge for subthreshold activation. As in Fig. 6B, initial hyperpolarization is due to the fact that initial *Erest* is set correctly for noise conditions. D: Control for C without Na+ channels. Slight hyperpolarization after initial transient on response is generated by delayed K+ channel activation.

tal amplitude of at least 5 mV and a rise time of less than the duration of the action potential (20 ms).

Importance of noise for circuit

Since the single-photon signal is much longer (100-200 ms rise time, Schnapf et al., 1994; Nelson, 1982) than the duration of action potential events (-20 ms), it would seem not an efficient stimulus (Figs. 6 and 7) for a subthreshold event. Activation of Hodgkin-Huxley Na+ channels is a function of both voltage level and duration of the stimulus, but in subthreshold mode the rate of rise of the stimulus determines how much activation occurs before Na+ inactivation and K+ activation starts (Hodgkin & Huxley, 1952). Therefore, higher-frequency noise peaks tended to initiate subthreshold events. When noise was present with a slow-rising photon event, virtually all subthreshold regenerative events were initiated by higher-frequency noise peaks riding on the slower photon event. Therefore, although one operation of the circuit is to reduce noise, a certain level of noise seems to be useful to "excite" the circuit to nonlinearly amplify slow events.

Since in our simulations there was a narrow range of Na+ and gap-junction conductances for which an event is amplified without generating a full action potential (thereby inducing the whole network to fire as well), we speculate that the cell's tendency to fire needs to be closely controlled. For example, the GABA- or glycine-induced chloride currents found by Boos et al. (1993) might be modulated in some way to oppose depolarization. Another possibility is that at scotopic intensities the AII coupling conductance might be up-modulated in some way

by the spiking activity of the neuron, thereby increasing the amount of noise averaging and reducing the tendency for the cell to generate spurious events. Such arrangements would in effect be a type of gain control by negative feedback.

Linearity of spatio-temporal summation

It seems possible that the ability to generate a subthreshold event is an adaptation by the AII to nonlinearly amplify the single-photon signal. One might wonder if the use of such a nonlinear mechanism would contradict the well-known observation that the ganglion cell's response is linear with small increments of intensity (e.g. Sakmann & Creutzfeldt, 1969). It does not because, while nonlinear transformations of a quantal photon signal change the ganglion cell's response amplitude, they do not affect the ability of the ganglion cell to spatio-temporally sum multiple photon events linearly. At higher intensities, though, where the AII temporally sums photon signals, noise due to the random capture of photons ("fluctuation noise") would obscure the single-photon signal so the threshold set in the AII for discriminating an isolated photon event would appear to be inappropriate. However, the AII might reduce the gain for photon signals (e.g. by modulating its coupling conductance or by negative synaptic feedback onto the AII, so its nonlinear amplification mechanism would be activated at a level that represented several photon signals. Thus, the AII's nonlinear mechanism might function in a "piecewise-linear" fashion over the entire scotopic range.

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