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Intrinsic properties and functional circuitry of the AII amacrine cell

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Abstract

Amacrine cells represent the most diverse class of retinal neuron, comprising dozens of distinct cell types. Each type exhibits a unique morphology and generates specific visual computations through its synapses with a subset of excitatory interneurons (bipolar cells), other amacrine cells, and output neurons (ganglion cells). Here, we review the intrinsic and network properties that underlie the function of the most common amacrine cell in the mammalian retina, the AII amacrine cell. The AII connects rod and cone photoreceptor pathways, forming an essential link in the circuit for rod-mediated (scotopic) vision. As such, the AII has become known as the rod-amacrine cell. We, however, now understand that AII function extends to cone-mediated (photopic) vision, and AII function in scotopic and photopic conditions utilizes the same underlying circuit: AII's are electrically coupled to each other and to the terminals of some types of ON cone bipolar cells. The direction of signal flow, however, varies with illumination. Under photopic conditions, the AII network constitutes a cross-over inhibition pathway that allows ON signals to inhibit OFF ganglion cells and contributes to motion sensitivity in certain ganglion cell types. We discuss how the AII's combination of intrinsic and network properties accounts for its unique role in visual processing.

Keywords

A2 amacrine cell; gap junction; glycinergic synapse; mouse; guinea pig; primate

The rod bipolar cell pathway in the mammalian retina

Psychophysical experiments in human subjects (Stiles, 1959; Alpern, 1965) and electrophysiological recordings from mammalian ganglion cells (Barlow *et al.*, 1957; Gouras & Link, 1966) demonstrated that threshold responses during rod- and cone-mediated vision are independent. This independence suggested that the outputs of the two photoreceptor types are conveyed to ganglion cells by distinct neural pathways. Such an arrangement was confirmed by the identification of rod- and cone-specific bipolar cells (Dowling & Boycott, 1966; Boycott & Dowling, 1969; Kolb, 1970; Boycott & Kolb, 1973). Though it was assumed initially that both rod and cone bipolar cells contacted ganglion cells directly (Boycott & Dowling, 1969), subsequent electron-microscopic (EM) analysis revealed that rod bipolar cells do not make synapses with ganglion cells; rather, rod bipolars provide synaptic input to a narrow-field, bistratified amacrine called the AII amacrine cell, which is the most common amacrine cell in the retina (Kolb & Famiglietti, 1974; Famiglietti & Kolb, 1975; Strettoi & Masland, 1996).

Today, the so-called rod bipolar cell pathway of the mammalian retina is well-described (Figure 1) (Bloomfield & Dacheux, 2001): rods make synapses onto rod bipolar cells, which depolarize in response to light. Rod bipolar cells make excitatory dyad synapses with two postsynaptic elements from separate neurons: AII and A17 amacrine cells (Famiglietti & Kolb, 1975; Dacheux & Raviola, 1986; Raviola & Dacheux, 1987). The A17 returns a GABAergic feedback synapse onto the rod bipolar terminal (Kolb & Nelson, 1983; Dacheux & Raviola, 1986; Raviola & Dacheux, 1987; Protti & Llano, 1998; Hartveit, 1999; Zhang *et al.*, 2002; Singer & Diamond, 2003; Chavez *et al.*, 2006). The AII, which is depolarized by input from the rod bipolar cell, is coupled by gap junctions to other AIIs and to the axon terminals of ON cone bipolar cells (Famiglietti & Kolb, 1975; Strettoi *et al.*, 1992; Strettoi *et al.*, 1994; Mills & Massey, 1995; Veruki & Hartveit, 2002b, a; Petrides & Trexler, 2008). The AII also makes inhibitory synapses onto the terminals of some OFF cone bipolar cells and onto the dendrites of some OFF ganglion cells (Pourcho & Goebel, 1985; Sterling *et al.*, 1988; Strettoi *et al.*, 1992; Tsukamoto *et al.*, 2001; Manookin *et al.*, 2008; Murphy & Rieke, 2008; Münch *et al.*, 2009). Thus, the AII distributes the rod signal to multiple parallel cone bipolar pathways. In effect, then, the rod bipolar pathway “piggybacks” on the cone pathways (Strettoi *et al.*, 1992). This arrangement likely arose to integrate rods, which are evolutionarily newer than cones, into existing retinal circuitry (Lamb, 2009).

Anatomy underlies the sensitivity of the rod bipolar pathway

Signaling in the rod bipolar cell pathway is remarkably sensitive and reliable. The circuit is capable of encoding a rod’s response to a single absorbed photon: the firing of a ganglion cell can be modulated by the absorption of a single photon within its receptive field, and the absorption of ~10 photons within the retina as a whole can generate a visual percept (Hecht *et al.*, 1942; Barlow *et al.*, 1971; Sakitt, 1972; Mastronarde, 1983; Field *et al.*, 2005). The sensitivity of ganglion cells to light arises from the *convergence* of thousands of rod outputs onto single ganglion cells: each rod bipolar cell pools the output of 20–100 rods, each AII receives input from 10–20 rod bipolars and makes electrical synapses with ~5 ON cone bipolar terminals (numbers vary with species and retinal location) (Dacheux & Raviola, 1986; Sterling *et al.*, 1988; Vaney *et al.*, 1991; Young & Vaney, 1991; Strettoi *et al.*, 1992; Tsukamoto *et al.*, 2001). Additionally, the *divergence* of a rod’s output to multiple neurons (1 rod → 2 rod bipolars → 5 AII → 8 ON cone bipolars) may increase the reliability with which the rod signal is transferred through the retina (Sterling *et al.*, 1988; Vaney *et al.*, 1991; Young & Vaney, 1991; Tsukamoto *et al.*, 2001). As noted by Sterling *et al.* (1988), divergence generates multiple copies of a rod’s signal that are transferred to a single ganglion cell by hundreds of ON cone bipolar cell synapses.

AII themselves are remarkably sensitive to light: in the dark-adapted retina, AII respond reliably to dim flashes of light sufficient to isomerize single rhodopsin molecules in fewer than 1 in 3 to 1 in 100 rods (varying by species) (Pang *et al.*, 2004; Trexler *et al.*, 2005; Dunn *et al.*, 2006). This sensitivity arises in part from the convergence of hundreds of rod outputs onto a single AII. Furthermore, electrical coupling between AII enhances the effective convergence of rods onto AII by permitting AII to be depolarized by rod bipolars that are not directly presynaptic (Sterling *et al.*, 1988; Bloomfield *et al.*, 1997; Pang *et al.*, 2004).

Gap junction-mediated coupling between AII can be demonstrated with the diffusion of tracer molecules. For example, Neurobiotin injected into a single AII spreads to neighboring AII, demonstrating cytoplasmic coupling (Vaney, 1991; Mills & Massey, 1995); this coupling, studied by light microscopy, confirms EM evidence for gap junctions between AII dendrites and somata (Kolb & Famiglietti, 1974; Famiglietti & Kolb, 1975; Strettoi *et al.*, 1992; Strettoi *et al.*, 1994; Vardi & Smith, 1996). These gap junctions are homomeric

protein complexes composed of connexin (Cx) 36 (Feigenspan *et al.*, 2001; Mills *et al.*, 2001; Deans *et al.*, 2002). The first evidence for functional electrical coupling between AII cells came from the work of Bloomfield *et al.* (Bloomfield *et al.*, 1997), who demonstrated that light-mediated modulation of receptive field size varied directly with light-mediated modulation of tracer coupling. Later, Veruki and Hartveit (Veruki & Hartveit, 2002a) recorded direct electrical coupling between pairs of AII cells in a retinal slice preparation [see also (Tian *et al.*, 2010)].

Gap junctions and signal processing

Though the convergence within the rod bipolar pathway in part underlies its sensitivity, convergence also increases the noise of neural responses by the square root of the number of inputs (Baylor *et al.*, 1984; Sterling *et al.*, 1988; Smith & Vardi, 1995). Gap junctions, by acting as low-pass filters, can average uncorrelated noise and improve the signal-to-noise ratio (S/N) in instances in which coupled cells receive correlated input (Lamb & Simon, 1976; Tessier-Lavigne & Attwell, 1988). Thus, it is thought that the AII network serves a noise-reducing role in rod-mediated vision.

A computational model of the AII network suggested that the network reduces noise in the rod bipolar pathway by filtering noise arising from spontaneous release at rod bipolar cell synapses and amplifying selectively light-evoked rod bipolar cell outputs that diverge to multiple coupled AII cells (Smith & Vardi, 1995). When the AII cells in the model lacked voltage-gated conductances (i.e., when they were passive neurons), their simulated responses to single photons could be differentiated from noise throughout a range of junctional coupling strength. Inclusion of voltage-gated conductances within the AII cells [noted first by (Boos *et al.*, 1993); also see (Tian *et al.*, 2010)] improved considerably the S/N of their simulated responses. Thus, the model indicated that a coupled network of AII amacrine cells with voltage-gated conductances might provide a mechanism for non-linear amplification of small, correlated signals during rod vision (Figure 2) (Smith & Vardi, 1995).

Experimental evidence has supported the first point made by the aforementioned study, that coupling within the AII network improves the sensitivity of AII cells: measured light-independent (i.e., background) noise was higher, and the S/N of light responses lower, in AII cells from mice that lack AII-AII gap junctions (Cx36 $-/-$ mice) relative to wild-type mice (Dunn *et al.*, 2006). Further, it is worth noting that direct measurements from AII cells indicated that the coupling conductances used in the modeling study were within the physiological range (albeit on the low end) (Veruki & Hartveit, 2002a; Veruki *et al.*, 2008).

Experiments, however, have not provided evidence for active amplification of correlated light-evoked signals by AII cells. In a light-adapted retinal slice preparation, Tian *et al.* (2010) found that voltage-gated Na channels can accelerate and, under some circumstances, boost the amplitudes of EPSPs recorded in AII cells and evoked by depolarizing single rod bipolar cells (Figure 3). But, in the same study, blocking voltage-gated Na channels with TTX did not reduce the amplitudes of light-evoked currents recorded in ganglion cells (though the light-evoked currents were slowed considerably). Thus, Na channels may shape the time course of signal transfer through the AII network but apparently do not influence the S/N of such signals. Indeed, Dunn *et al.* demonstrated that the gain of dim light-evoked AII voltage and current responses (current- and voltage-clamp recordings, respectively) scaled identically with background, indicating that postsynaptic amplification of RB output, at least at the level of individual AII cells, does not play a role in increasing S/N (Dunn *et al.*, 2006).

Modulation of coupling

AII-AII coupling is modulated by background light. In the dark-adapted condition, the AII's receptive field is small (~50 μm , 2–3 times the diameter of its dendritic tree) (Bloomfield *et al.*, 1997; Xin & Bloomfield, 1999; Bloomfield & Xin, 2000). The receptive field size increases (up to several hundred μm) with background illumination through the scotopic regime before the size diminishes again at photopic intensities (Bloomfield *et al.*, 1997). Parallel changes in tracer coupling between AIIs are observed with changes in background illumination. Hence, the dependence of receptive field size on background apparently reflects a background-dependent change in electrical coupling between AIIs, which has been postulated to gate signal transfer between the rod and cone pathways (Bloomfield *et al.*, 1997). The reduced coupling between AIIs at photopic intensities is thought to limit the lateral spread of neural signals in the inner retina, thereby improving the spatial acuity of bipolar, amacrine and ganglion cell receptive fields.

Light is thought to affect AII-AII coupling by modulating the release of the neuromodulator dopamine (DA) from dopaminergic amacrine cells (Witkovsky, 2004). Although it was observed that DA, acting through D1 receptors (D1Rs), reduces tracer coupling between AIIs (Hampson *et al.*, 1992), the mechanism by which this occurs is uncertain. It is well-known that activation of D1Rs induces cAMP production by activating PKA (Schorderet & Nowak, 1990; Neve *et al.*, 2004), and predictably, direct activation of PKA and application of membrane-permeant cAMP analogs mimic the DA effect (Mills & Massey, 1995; Xia & Mills, 2004; Urschel *et al.*, 2006; Kothmann *et al.*, 2009). Additionally, the DA- and cAMP-regulated phosphoprotein 32 kDa (DARPP-32) is expressed by AIIs (Partida *et al.*, 2004; Witkovsky *et al.*, 2007). DARPP-32 is phosphorylated at multiple sites by a number of signaling pathways that are activated by D1R activation, and DARPP-32 phosphorylation can either promote or inhibit phosphorylation of other proteins by modulating the activity of PP1 and PKA (Svenningsson *et al.*, 2004).

Initial studies suggested that DA does not modulate AII-ON cone bipolar tracer coupling (Mills & Massey, 1995), which appears to be mediated by heteromeric Cx36 / Cx45 gap junctions (Han & Massey, 2005; Maxeiner *et al.*, 2005; Dedek *et al.*, 2006). Further quantitative analysis indicated that tracer coupling between these two cell types indeed is suppressed by DA, and that the strength of AII-ON cone bipolar coupling should therefore be reduced in daylight (Xia & Mills, 2004). Physiological evidence, however, suggests that the AII-ON cone bipolar gap junction continues to function as an electrical synapse in the light-adapted retina (Xin and Bloomfield, 1999; Manookin *et al.*, 2008; Münch *et al.*, 2009). Therefore, it will be necessary to measure directly whether the conductance of the AII-ON cone bipolar gap junction in the intact retina is modulated by light.

Two competing and conflicting hypotheses have been advanced to link D1R activation to the modulation of gap junctions: 1) PKA induced phosphorylation of Cx36, likely at serines 110 and 293, decreases gap junction conductance (Urschel *et al.*, 2006), and 2) DA-stimulated dephosphorylation of Cx36 at serine-293 decreases gap junction conductance (Kothmann *et al.*, 2009). This dephosphorylation is mediated by the activation of protein phosphatase 2A (PP2A) activation by PKA; this signaling pathway is likely complex, as PP2A also dephosphorylates DARPP-32 at Thr⁷⁵, thereby promoting inhibition of PKA (Svenningsson *et al.*, 2004).

Adding to the uncertainty surrounding the relationship between D1R activation and the modulation of AII-AII coupling is the lack of evidence for D1R expression by AIIs: antibody labeling finds no D1R in AIIs (Veruki & Wässle, 1996) [but see (Nguyen-Legros *et al.*, 1997)], and AIIs do not express GFP (green fluorescent protein) in BAC (bacterial

artificial chromosome) transgenic mice in which the D1R promoter drives GFP expression (J. Singer, unpublished observations). Further, direct application of either dopamine or D1R agonists and antagonists does not affect junctional conductances recorded in pairs of AII's in an *in vitro* retinal slice preparation (J. Singer, unpublished observations). Thus, additional work is required to elucidate the localization and function of D1Rs as they relate to modulation of AII-AII coupling.

Selective network connections: ON cone bipolar cells

The AII's dendrites span the entire depth of the inner plexiform layer enabling potential contact with numerous types of bipolar, amacrine and ganglion cell. Only a subset of each cell class, however, actually connects with the AII. High resolution analysis of the cat retina by serial EM revealed that the AII avoids making gap junctions with two types of ON cone bipolar cell (b3, b5) and forms unequal numbers of gap junctions with the remaining types (McGuire *et al.*, 1984; Cohen & Sterling, 1990). The AII made a large number of gap junctions with the b1 type and 7–8-fold fewer contacts (based on surface area) with b2 and b4 types. Furthermore, the b3 type, which lacked a direct connection, was connected effectively to the AII through b3-b4 gap junctions (Cohen & Sterling, 1990) (Figure 4A).

Complementary light-microscopic studies have been performed in the rabbit retina using tracer coupling and anti-glycine immunohistochemistry. Glycine labeling implies coupling because glycine only enters ON cone bipolar cells through their gap junctions with AII's (i.e., the bipolar cells do not express glycine transporters; Vaney *et al.*, 1998). These experiments suggested that one (unknown) bipolar type lacked any connection to the AII, while one of the remaining bipolar types (calbindin-immunoreactive; calbindin⁺) showed a dominant connection (Petrides & Trexler, 2008; Massey & Mills, 1999). EM analysis confirmed that the calbindin⁺ type makes numerous gap junctions with AII's; whereas another type (neurokinin 1 receptor-immunopositive; NK1R⁺) makes fewer junctions (Massey & Mills, 1999; Kim *et al.*, 2005; 2010). An electrophysiological assessment of AII-ON cone bipolar coupling in rat retina found that four types of ON cone bipolar cell were coupled to AII's, but it was not possible to rank-order the connection strengths by cell type (Veruki & Hartveit, 2002b).

The ON cone bipolar cell with the strongest connection to the AII is that type presynaptic to the ON Alpha ganglion cell: the b1 type in cat (Freed & Sterling, 1988; Cohen & Sterling, 1990) and the calbindin⁺ type in rabbit (Massey & Mills, 1996; 1999; Strettoi *et al.*, 1994; Zhang *et al.*, 2005) (Figure 4A). ON Alpha ganglion cells are highly sensitive under scotopic conditions; presumably, this can be attributed to the strong coupling between their presynaptic bipolar cells and the AII network (Müller *et al.*, 1988; Dunn *et al.*, 2006; Murphy & Rieke, 2006).

In the cat retina, the ON cone bipolar cell with the weakest connection to the AII was the b5 cell presumed to be a specialized 'S-cone bipolar cell,' with selective input from S-cones: the 5% of cones with peak sensitivity to short-wavelength (S) light. Thus, highly sensitive scotopic signals would apparently not reach those ganglion cells postsynaptic to S-cone bipolar cells. Primate small-bistratified ganglion cells, however, receive input from S-cone bipolar cells and display responses mediated by the rod bipolar/AII amacrine pathway (Crook *et al.*, 2009; Field *et al.*, 2009). Furthermore, primate S-cone bipolar cells showed apparent contacts with AII cells, as determined by immunohistochemistry and confocal microscopic analysis (Field *et al.*, 2009). Thus, the AII cell connections to the ON cone bipolar cells apparently are weighted differently by cell type with the specific pattern of connections differing between species.

Selective network connections: OFF cone bipolar cells

As with their connections to the ON pathway, AII make synapses with only a subset of OFF bipolar cells. In the mouse retina, for example, EM analysis showed that AII lobular appendages, the sites of glycine release, are presynaptic to a B1 OFF bipolar cell type but not a B2 type (Tsukamoto *et al.*, 2001). Interestingly, the B1 type received input at its dendrites only from cone photoreceptors, whereas the B2 type, despite its label as a 'cone bipolar cell,' received input from both cones and rods (Figure 4A). This combined connectivity with both cones and rods was identified as a 'tertiary rod pathway' through certain bipolar cell types (Soucy *et al.*, 1998; Hack *et al.*, 1999; Tsukamoto *et al.*, 2001; Li *et al.*, 2004; Tsukamoto *et al.*, 2007). The differences between B1 and B2 types suggest that some OFF bipolars may be connected to either the 'primary rod pathway' (i.e., the AII circuit) or the tertiary rod pathway (i.e., direct rod input) but not both. All bipolar types presumably would receive signals through the 'secondary rod pathway,' whereby rods signal through gap junctions with cones and then through chemical synaptic input to cone bipolar cells (Nelson, 1977; Smith *et al.*, 1986; Schneeweis & Schnapf, 1995).

In cat, AII avoid contacting certain OFF cone bipolar cell types (CBa2, CBa3) but do contact others (CBa1, CBa4; McGuire *et al.*, 1984). The CBa1 cell seemed to be specialized among the OFF bipolars, similar to the cat's ON b1 bipolar, to receive dominant input from the AII. Not only does the CBa1 cell receive input from the AII, it also makes reciprocal ribbon synapses onto the AII; these reciprocal synapses provide a mechanism for OFF bipolar cells to excite the AII at light offset (McGuire *et al.*, 1984). Indeed, similar reciprocal synapses were observed in rabbit (DAPI-Ba2 cell type; Strettoi *et al.*, 1992; Merighi *et al.*, 1996), rat (Chun *et al.*, 1993) and primate (DB3 cell type; Jacoby & Marshak, 2000; Wässle *et al.*, 1995) (Figure 4A).

The function of reciprocal AII-OFF bipolar cell synapses, however, requires further study: although the AII's light response shows an OFF response component at an early stage of light adaptation (rabbit; Xin & Bloomfield, 1999), its ON response component dominates under most conditions (Nelson, 1982; Dacheux & Raviola, 1986; Pang *et al.*, 2007; Murphy & Rieke, 2008). Thus, although synaptic transmission between OFF cone bipolars and AII has been demonstrated electrophysiologically (Veruki *et al.*, 2003), the relevance of such transmission during physiological responses to light is uncertain.

Selective network connections: OFF ganglion cells

The AII could, in theory, signal to the ON and OFF pathways exclusively via its contacts with bipolar cell terminals. The AII, however, also makes direct chemical synapses onto the dendrites of a few OFF ganglion cell types (Manookin *et al.*, 2008; Murphy & Rieke, 2008; Münch *et al.*, 2009; Anderson *et al.*, 2011). For example, OFF Alpha/Transient and OFF Delta/Sustained cells in both mouse and guinea pig appear to receive direct inputs from the AII because firing in scotopic conditions is driven primarily by the modulation of inhibitory glycinergic synapses (Murphy & Rieke, 2006; Manookin *et al.*, 2008; Beaudoin *et al.*, 2008; van Wyk *et al.*, 2009).

Paired-cell recordings demonstrated directly a synapse between AII and OFF Alpha cells in the mouse (Murphy & Rieke, 2008; Münch *et al.*, 2009). In the guinea pig, pharmacological manipulations confirmed the role for the AII in modulating Alpha and Delta cell responses (Manookin *et al.*, 2008; Beaudoin & Demb, unpublished observations). In cat, EM analysis showed that both OFF Alpha and Beta cells receive direct AII input, and for Alpha cells, the number of AII contacts about equaled the number of OFF cone bipolar contacts (Kolb & Nelson, 1993; Owczarzak & Pourcho, 1999). Similar contacts with a select number of

ganglion cells were also observed in rabbit (Strettoi *et al.*, 1992; Anderson *et al.*, 2011) and rat (Chun *et al.*, 1993).

The AII contributes to network function under photopic conditions

Under photopic conditions, when rod bipolar signaling is saturated, light stimulation of cones depolarizes ON cone bipolar cells, which then can depolarize coupled AII. The direction of signaling (ON cone bipolar \rightarrow AII; Figure 4B) is reversed relative to that under scotopic conditions (AII \rightarrow ON cone bipolar; Figure 1). Thus, depolarization of the AII under photopic conditions should not require a conventional ionotropic glutamate receptor (iGluR; i.e., AMPA, kainate or NMDA channel), in contrast to all other known circuits in the retina. Indeed, photopic AII light responses persist in the presence of iGluR antagonists that block the conventional retinal pathways (Xin & Bloomfield, 1999; Trexler *et al.*, 2005; Pang *et al.*, 2007). Furthermore, AII inhibition of OFF ganglion cells (Alpha, Beta and Delta types) persists in bright light in the absence of iGluR function through the following circuit: cone \rightarrow ON cone bipolar \rightarrow AII amacrine \rightarrow OFF ganglion cell (Figure 4B) (Cohen, 1998; Cohen & Miller, 1999; Beaudoin *et al.*, 2008; Manookin *et al.*, 2008; Münch *et al.*, 2009). These results show that the ON cone bipolar-AII gap junction functions in bright light allowing AII cells to contribute to vision under photopic conditions.

Computational role in photopic vision

In the ON pathway, the functioning gap junction between ON cone bipolar cells and AII should degrade spatial acuity in bright light (Mills & Massey, 1995). Since certain bipolar pathways show little or even no contact with the AII network (Figure 4A), the impact of electrical coupling on spatial acuity should vary between parallel cone bipolar cell pathways.

In the OFF pathway, the AII plays several roles in vision under photopic conditions. Tonic release of glycine by the AII helps to set the resting potential of both OFF bipolar and ganglion cells as well as the basal release rate of glutamate from OFF bipolar terminals (Zaghloul *et al.*, 2003; Margolis & Detwiler, 2007; Liang & Freed, 2010). Glycinergic modulation of OFF bipolar terminals increases the operating range of glutamate release (Liang & Freed, 2010). Additionally, certain OFF ganglion cell types integrate AII-mediated inhibition and OFF bipolar cell-mediated excitation (Figure 5). Thus, the AII generates cross-over inhibition from the ON pathway to the OFF pathway that competes with OFF pathway excitation. At light onset, the AII compensates for the rectifying OFF bipolar cell synapses by generating hyperpolarizing responses in the ganglion cell (Demb *et al.*, 2001a; Zaghloul *et al.*, 2003; Molnar *et al.*, 2009; Werblin, 2010). At light offset, tonic release of glycine from the AII is suppressed, and the resulting 'disinhibition' of the ganglion cell combines with conventional excitation from OFF bipolar cells to extend the operating range for encoding negative contrasts (Manookin *et al.*, 2008). Thus, the AII signals OFF bipolar terminals and OFF ganglion cells through both increases and decreases from a tonic level of glycine release.

There are two possible computational advantages to combining inhibition and excitation at the ganglion cell. First, the AII's inhibition can compete with the OFF bipolar cell's excitation at the scale of the ganglion cell's wide dendritic tree (hundreds of microns). By contrast, AII inhibition of OFF bipolar cell terminals will have little effect if the adjacent OFF bipolars are not active (i.e., because the OFF bipolar cell release rate is commonly rectified and cannot be decreased below zero); therefore, AII inhibition at OFF bipolar terminals is limited to local interactions where simultaneous excitation and inhibition compete over a narrow spatial scale (i.e., tens of microns). Second, postsynaptic inhibition acts in the presence of high release rates from bipolar and amacrine cell terminals. The high release rates convey signals with high S/N to the ganglion cell (assuming release rates are

governed by Poisson statistics). This contrasts with the presynaptic locus of inhibition (AII→OFF cone bipolar terminal), where the release onto the ganglion cell is only excitatory and is suppressed in the presence of inhibition, resulting in signals with low S/N.

The competition between OFF pathway bipolar cell-mediated excitation and ON pathway AII-mediated inhibition tunes the OFF ganglion cell response to different forms of motion. A drifting grating represents first-order motion, defined by spatio-temporal changes in luminance. A low spatial-frequency grating will alternately stimulate OFF pathway excitation when dark bars pass over OFF bipolar cells and ON-pathway inhibition when light bars pass over ON bipolar cells and their coupled AII amacrine cells (Figure 5C). A high spatial-frequency grating will simultaneously excite both OFF excitatory and ON inhibitory inputs. This simultaneous stimulation of the two pathways leads, in some cases, to a tonic elevation in firing when the excitatory inputs are relatively stronger (Cleland *et al.*, 1971; Manookin & Demb, 2006). Likewise, a contrast-reversing grating activates both pathways simultaneously, but the excitation dominates, resulting in a burst of firing at each contrast reversal (Figure 5B) (Hochstein and Shapley, 1976; Demb *et al.*, 2001a). Thus, in these cases the AII-mediated inhibition attenuates the effect of excitation, preventing excessive depolarization, but does not cancel it. The recordings mentioned above were made in cat or guinea pig cells. In the mouse retina, however, the response to a drifting high spatial frequency grating showed that the AII and OFF bipolar inputs canceled one another and the ganglion cell did not fire (Münch *et al.*, 2009). Thus, the combined OFF bipolar/AII circuit has the potential to cancel responses selectively at high spatial frequencies. The degree of cancellation may depend on certain stimulus conditions (i.e., level of light adaptation) or may differ between species.

A second-order motion stimulus is defined by spatio-temporal changes in contrast (Figure 5C). As a low contrast window moves and reveals a stationary, high contrast grating pattern, the combined OFF excitatory and ON inhibitory inputs modulate the membrane potential around rest, driving bursts of firing (Demb *et al.*, 2001b; Rosenberg & Issa, 2010) (the source of inhibition in the earlier study was not identified as the AII, but we now understand this to be the case [Manookin *et al.*, 2008]). Finally, an expanding dark stimulus yields a strong response in OFF Alpha ganglion cells, because local OFF bipolar cells are excited as AII cells are simultaneously suppressed (Münch *et al.*, 2009) (Figure 5C). It has been proposed that this response to approaching motion might be important for certain behaviors (e.g., avoiding an approaching back-lit object or predator).

Concluding remarks

The existence of gap junction-mediated coupling between AII is well-established, as is the modulation of this coupling by ambient light and DA. However, it is not immediately apparent why coupling between AII is necessary for ganglion cell processing of rod signals. Because AII are coupled to ON cone bipolar terminals, rod signals arising in the AII's dendrites will be integrated by the ganglion cells postsynaptic to the ON cone bipolar terminals even if AII are not coupled to each other. The AII-ON cone bipolar cell gap junctions would serve to filter noise, and the voltage-gated Ca channels in the bipolar cell terminals would amplify rod signals nonlinearly. Similarly, OFF ganglion and bipolar cells postsynaptic to AII will receive glycinergic input even in the absence of AII-AII coupling, and chemical synaptic transmission is an inherently nonlinear process owing to the dependence of exocytosis on two nonlinear processes: voltage-dependent Ca channel gating and Ca²⁺ activation of the vesicular release machinery. To fully appreciate the roles of these processes, we need to better understand the dynamics of transmission at the AII's glycinergic synapses. Furthermore, it is possible that there are undiscovered advantages to having two sites of coupling that could be modulated independently.

Additionally, the primary site of noise reduction in the rod bipolar pathway occurs upstream of the AII, at the rod → rod bipolar synapse (Dunn *et al.*, 2006). A postsynaptic thresholding mechanism arising from saturation in the second messenger cascade linking glutamate receptor activation with membrane conductance serves to eliminate the majority of rod noise from rod bipolar cell signals (van Rossum & Smith, 1998; Field & Rieke, 2002; Sampath & Rieke, 2004). Indeed, noise measured in AII is actually much greater than that in rod bipolar cells (Dunn *et al.*, 2006). This noise arises at the rod bipolar → AII synapse, which operates at high gain (Dunn *et al.*, 2006), likely owing to the high release probability of vesicles (Singer *et al.*, 2004; Jarsky *et al.*, 2010). Thus, noise is a consequence of this high gain. Both the gain and noise in ganglion cell responses match that of the AII and are 4–6 times that which would arise from noiseless summation of rod output in the rod bipolar pathway. Hence, the noise in ganglion cell responses is apparently inherited from noise in AII (Dunn *et al.*, 2006). This noise in the ganglion cells might be even higher if AII were uncoupled.

It will be informative to determine whether the pattern of AII synapses, investigated by EM, can predict the function of parallel pathways during night vision. We might then understand why certain ganglion cell types are more sensitive than others under scotopic conditions (Purpura *et al.*, 1988; Lee *et al.*, 1997; Deans *et al.*, 2002; Völgyi *et al.*, 2004). Understanding the role of AII cells in specific perceptions and behaviors will ultimately require methods for reversibly inactivating these cells. For example, one could test whether avoidance of approaching dark stimuli is lost following inactivation of AII cells (Münch *et al.*, 2009). There are several types of narrow-field glycinergic amacrine cell other than the AII (Wässle *et al.*, 2009), and so it will be interesting to learn whether there is enough redundancy in retinal circuitry such that certain behaviors survive inactivation of single amacrine cell types.

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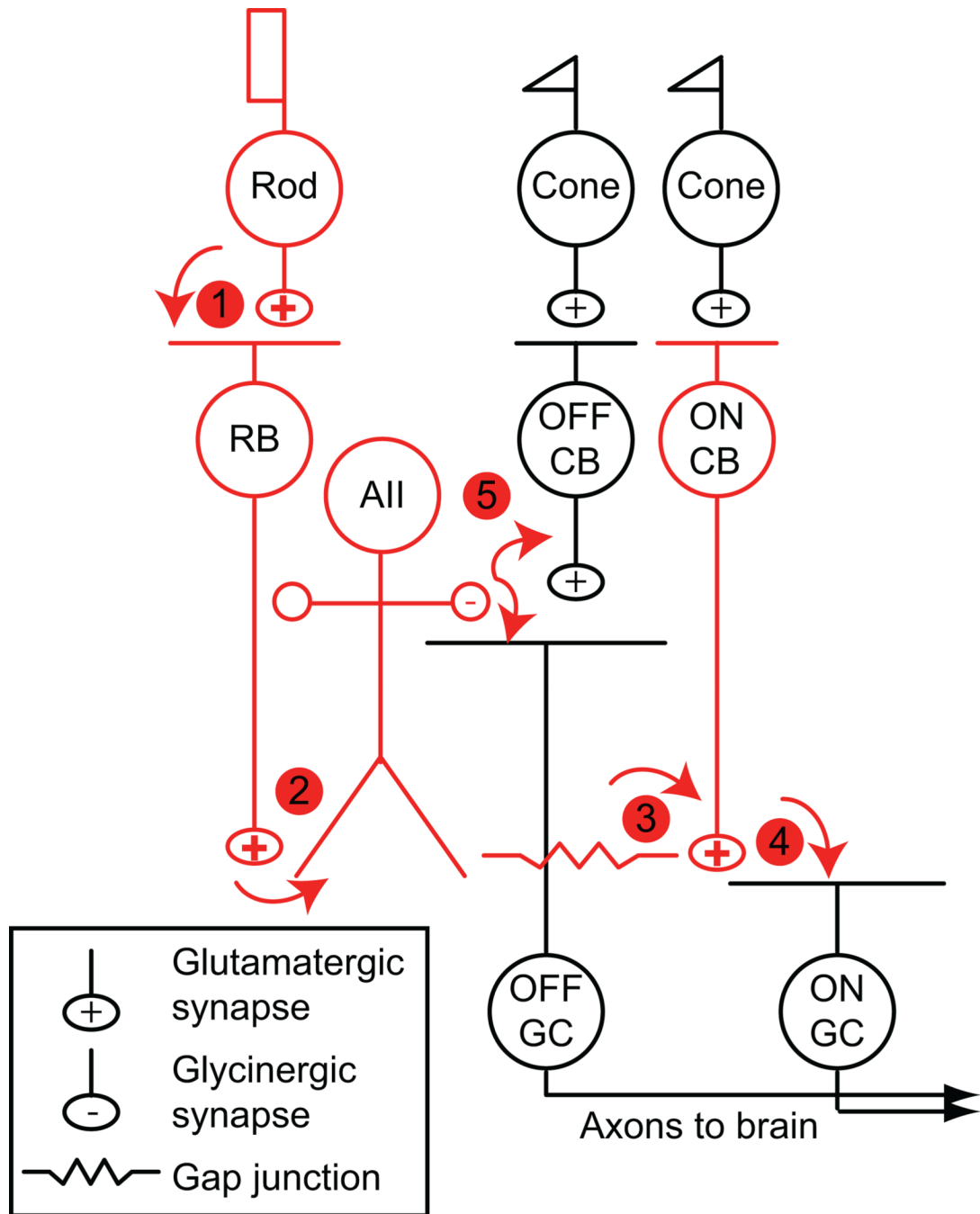


Figure 1. The rod bipolar pathway of the mammalian retina

Principal neurons are colored red and synapses are numbered. Cones make synapses with two classes of cone bipolar cell (CB): ON and OFF CBs. ON and OFF CBs make excitatory synapses with ganglion cells (GCs), the output cells of the retina.

(1) Rods make synapses with an ON bipolar cell, the rod bipolar (RB), and with a subset of OFF CBs (not shown). Gap junctions between rods and cones are not illustrated (Raviola & Gilula, 1973; DeVries & Baylor, 1995).

(2) RBs contact AII amacrine cells.

(3) AIIs are coupled by gap junctions to some types of ON CBs and to other AII.

(4) ON CBs make synapses with ON GCs.

(5) AIIs make inhibitory glycinergic synapses with some OFF CBs and OFF GCs.

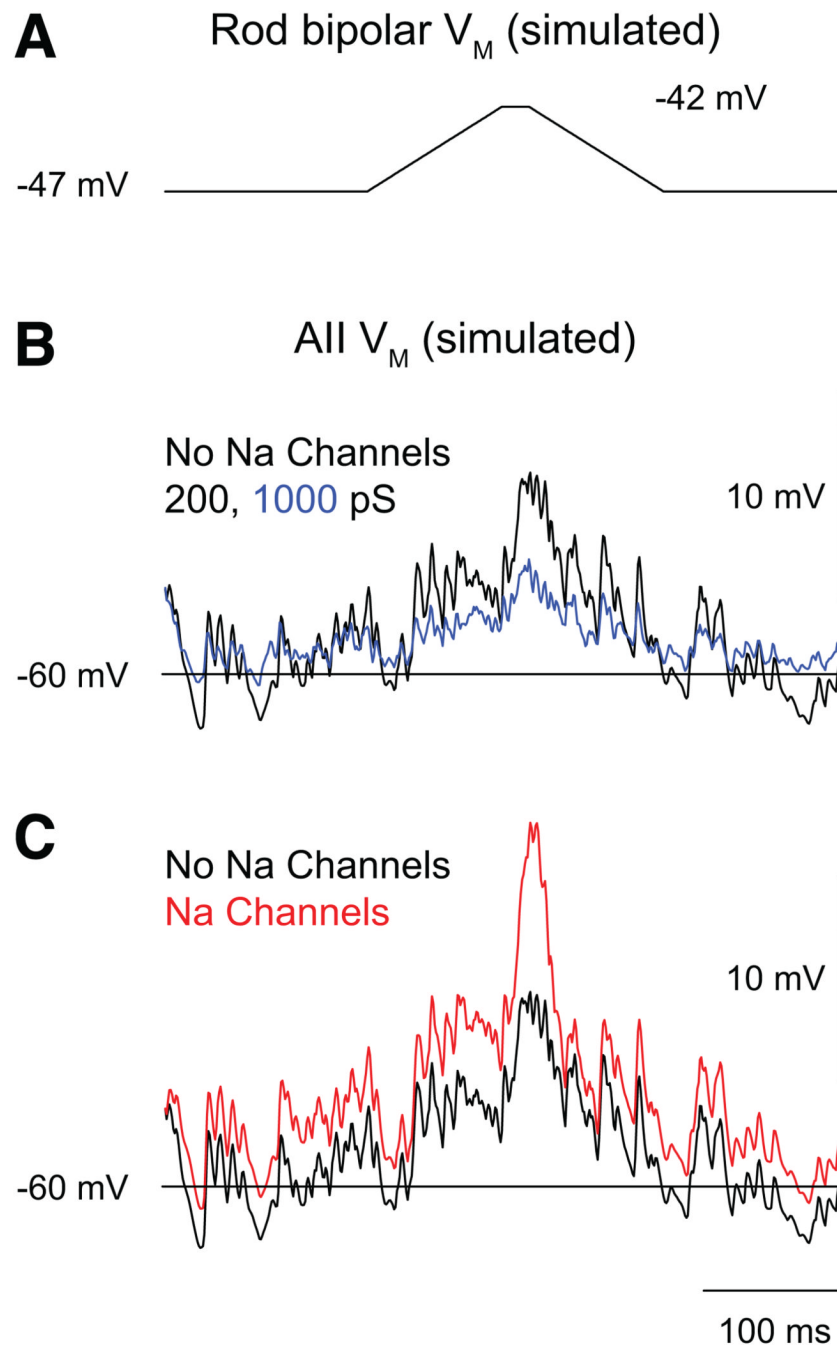


Figure 2. A computational model of the AII network predicts effects of coupling strength and Na channel expression on postsynaptic responses to divergent rod bipolar output

(A) The voltage change in a single rod bipolar cell elicited by a “single-photon” response. The cell’s synaptic output diverges to five coupled AII amacrine. (B) the postsynaptic responses elicited when coupling strength (black = junctional conductance of 200 pS; blue = junctional conductance of 1000 pS) is altered. (C) the postsynaptic responses elicited when Na channel expression (black = no Na channels; red = Na channels present; junctional conductance = 200 pS) is varied. It is evident that the postsynaptic response is larger when the coupling conductance is low and Na channels are present. Figure modified from (Smith and Vardi, 1995).

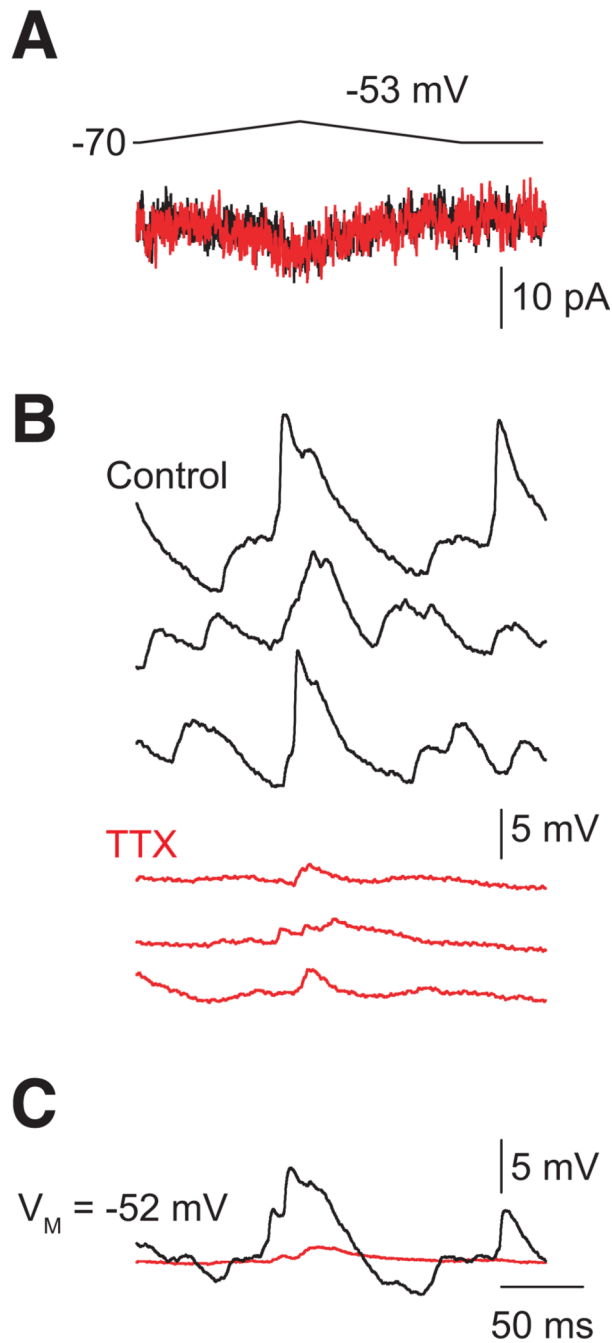


Figure 3. Representative AII responses to rod bipolar output

Minimal presynaptic depolarization (to -53 mV at left) elicits presynaptic Ca currents (A) and EPSPs (B: individual responses; C: averaged responses). EPSPs evoked by minimal stimulation are reduced substantially by TTX. TTX has no effect on the presynaptic Ca current. TTX also eliminates fluctuations in V_M . Figure modified from (Tian *et al.*, 2010).

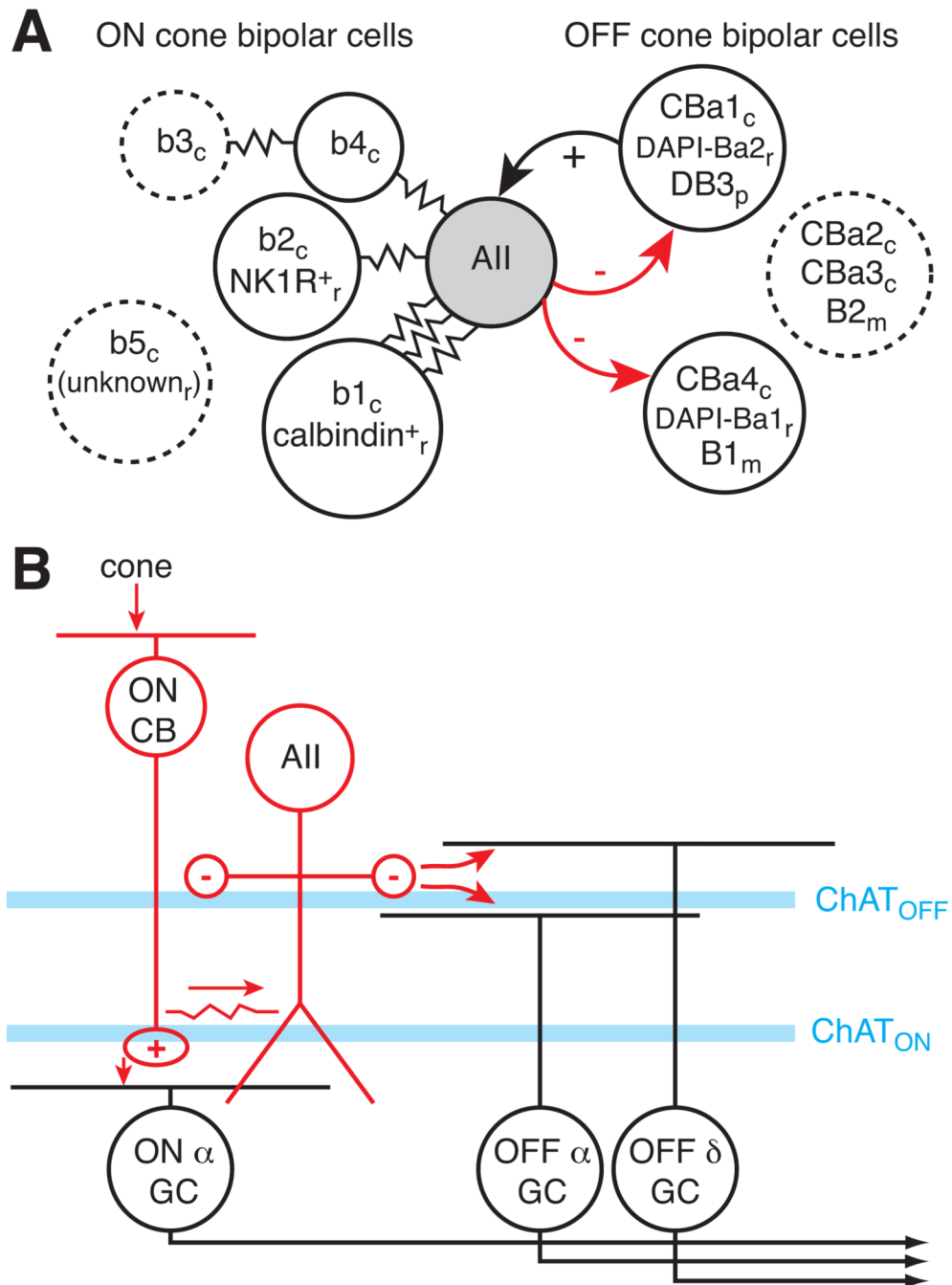


Figure 4. Selective connections of the AII amacrine cell

(A) Schematic diagram indicates the gap junction coupling (resistor symbols) for different bipolar cell types. In most cases, connections were identified by EM and cell type names are from the original studies (see text). Species are indicated by subscript letter (c=cat; r=rabbit; m=mouse; p=primate). Cell types that were not directly connected to the AII are outlined with a dashed line.

(B) Photopic circuit for AII signaling. When the rod bipolar cell (not shown) saturates in bright light, cones stimulate ON cone bipolar cells, which excite the AII through the gap junction. The AII can then inhibit, via a glycine synapse, two OFF ganglion cell types: Alpha and Delta, which stratify on different sides of the cholinergic band (immunopositive

for choline acetyltransferase; ChAT) in the outer half of the inner plexiform layer (i.e., the OFF ChAT layer). The AII could also inhibit certain types of OFF cone bipolar cell (not shown).

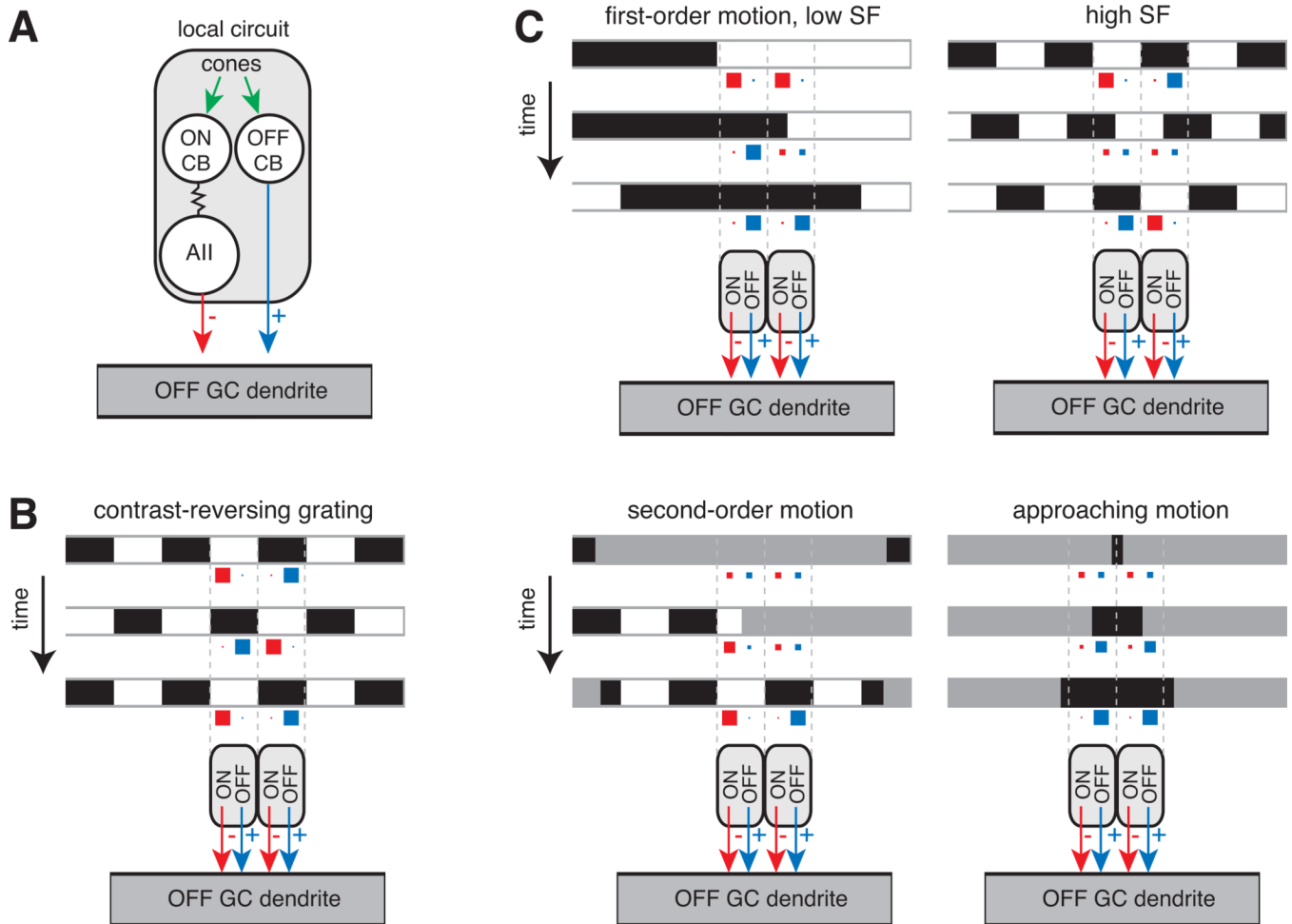


Figure 5. Function of the AII in motion detection

(A) A local circuit is formed by an OFF cone bipolar cell paired with an ON cone bipolar cell that signals through the AII. Both the OFF bipolar and AII converge on the ganglion cell dendrite. This local circuit is summarized in parts (B) and (C) as an OFF-pathway excitatory input (black arrow) paired with an ON-pathway inhibitory input (red arrow).

(B) Contrast-reversing grating: a high spatial-frequency grating reverses contrast over time. Image frames are shown at three time points. The level of inhibition (red) and excitation (blue) in each of two local circuits is illustrated by the size of squares: larger squares represent higher release rates. On each frame, excitation in one region combines with inhibition in the neighboring region. The summed activity typically results in a burst of firing at each grating reversal showing that excitation dominates (see text).

(C) First-order motion: a drifting grating is shown for both low and high spatial frequency (SF) stimuli. Bars move rightward and stimulate both OFF bipolar and AII amacrine cell release. At the low spatial frequency, excitation and inhibition alternate; whereas at the high spatial frequency, excitation and inhibition co-occur. In different experiments (see text), the high spatial frequency stimulus generates either a net excitation or a cancellation at the ganglion cell level.

Second-order motion: a stationary grating's contrast is modulated by a moving contrast boundary. The OFF bipolar and AII cell are stimulated as the low contrast boundary moves rightward, revealing the underlying stationary grating. The combination of these inputs generates a modulation of membrane potential around rest and drives firing (see text).

Approaching motion: a small dark stimulus expands over time. The stimulus drives increased release from OFF cone bipolars while suppressing release from AIIIs leading to high firing rates in the ganglion cell (see text).