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The diverse functional roles and regulation of neuronal gap junctions in the retina

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Abstract

Electrical synaptic transmission through gap junctions underlies direct and rapid neuronal communication in the CNS. The diversity of functional roles that electrical synapses have is perhaps best exemplified in the vertebrate retina, in which gap junctions are formed by each of the five major neuron types. These junctions are dynamically regulated by ambient illumination and by circadian rhythms acting through light-activated neuromodulators such as dopamine and nitric oxide, which in turn activate intracellular signalling pathways in the retina. The networks formed by electrically coupled neurons are plastic and reconfigurable, and those in the retina are positioned to play key and diverse parts in the transmission and processing of visual information at every retinal level.

Rapid inter-neuronal communication is fundamental to the integration and propagation of signals in the brain. Although chemical synaptic transmission is the most common mode of neuronal communication, demonstrations of direct electrical signalling between neighbouring neurons date back more than 50 years^{1,2}. It was shown subsequently that electrical synapses are specializations of closely opposed membranes called gap junctions^{3,4}, but there remained a paucity of studies of electrical synaptic transmission owing to the difficult and laborious techniques that were needed to show the existence of direct electrical interactions or to visualize gap junction profiles. Over the past decade, however, there has been a proliferation of investigations of electrical transmission and gap junctions owing to new techniques, including the use of gap junction-permeable tracers, patch recordings and molecular cloning. Possibly the most important finding was the discovery of the connexin subunit structure of gap junctions (fig. 1). Connexins can be identified through immunocytochemical techniques to determine the distribution of gap junctions in the brain⁵. Further, the use of mouse mutants in which selected gap junctions are disrupted by targeting connexin genes has become an important tool by which to characterize the function of electrical synapses.

It is now clear that electrical synaptic transmission through gap junctions is a common mode of inter cellular communication in the CNS⁶. An elegant example of such communication is provided by the vertebrate retina, in which each of the five major neuron types is coupled by gap junctions that express a number of different connexin proteins^{5,7}. In many cases the coupling strength is regulated by ambient illumination or circadian rhythms acting through neuromodulators^{8–12}. Gap junctions' broad distribution, subunit makeup and regulatory pathways suggest that they have a number of key and diverse functional roles relating to neural processing of images. In this regard the retina serves as arguably the best model system in which to study the functional roles of neuronal gap junctions and electrical

transmission in the CNS. In this Review we describe seven distinct functional roles that have been elucidated for retinal gap junctions, related not only to the propagation of signals, but also to the encoding of specific visual information. These findings indicate that electrical synapses play a complex part in neural signalling in the brain, with their regulation and plasticity rivalling those described for chemical transmission.

Structure and regulation of gap junctions

Gap junctions, the morphological substrate of electrical synapses, are composed of two hemichannels, or connexons, that link across an extracellular space of 2–4 nm (fig. 1a). They form a channel that directly communicates with the cytoplasm of neighbouring cells, providing an intercellular pathway for the diffusion of molecules up to 1,000 Da. Hemichannels are in turn composed of six transmembrane protein subunits called connexins, approximately 20 different isoforms of which have been characterized in humans and mice^{7,13}. A hemichannel can be composed entirely of one connexin (homomeric) or can be composed of different connexin types (heteromeric), although it seems that only certain connexins can combine to form functional hemichannels. In addition, a gap junction can be composed of two hemichannels with the same (homotypic) or different (heterotypic) connexin makeup.

Similar to ion channels, the conductance of gap junctions is regulated by a number of physiological factors and agents. Most gap junction connexins undergo post-translational modification by phosphorylation — mainly of serine amino acids found in their carboxyl termini and intracellular loop regions^{14,15} (Fig. 1b). Indeed, connexins are targeted by numerous protein kinases and the resulting phosphorylation has been implicated in a broad range of regulatory steps, including trafficking, assembly and disassembly, and conductance gating of gap junctions. These protein kinases are modulated by a number of factors, including Ca^{2+} -calmodulin, cyclic AMP, cyclic GMP and neuromodulators.

Importantly, the light-activated neuromodulators dopamine and nitric oxide (NO), which are released by different amacrine cell subtypes^{16,17}, activate a number of intracellular pathways involving cAMP- and cGMP-dependent protein kinases. This results in the phosphorylation or dephosphorylation of gap junction connexins, altering the conductance of the gap junctions to ionic currents^{18–21} (Fig. 2). This modulation varies across the population of retinal interneurons, such that the conductance of some gap junctions is increased by light whereas that of others is decreased^{10,11,22–26}. In fact, light can increase or decrease the conductance of gap junctions in the same neuron, depending on the level of brightness^{8,10,25,26}.

It has long been known that increases in cytosolic Ca^{2+} can close gap junctions^{27,28}. Recent studies indicate that Ca^{2+} action on gap junction conductance is dependent on calmodulin, which interacts directly with connexin subunits^{19,20,29,30}. Consistent with this idea, inhibition of calmodulin prevents the Ca^{2+} -mediated reduction in cell coupling through actions on a number of different connexins, including CX43 (also known as GJA1) and CX32 (also known as GJB1)^{30–32}.

Subtle changes in intracellular pH can also alter the electrical coupling between neurons^{33,34}. Acidification usually results in decreased conductance of certain gap junctions, whereas alkalization produces a conductance increase; however, in sharp contrast to other connexins, the conductance of CX36 (also known as GJD2) gap junctions decreases after alkalosis rather than acidosis³⁵. Because neural activity produces changes in intracellular pH³⁶, the proton sensitivity of gap junctions provides a mechanism for activity-dependent modulation of coupling between neighbouring neurons.

Finally, most mammalian gap junctions are sensitive to the voltage difference across the junctional membrane^{37,38}, the parameters of this sensitivity varying according to the connexin expressed. This sensitivity is a second mechanism by which gap junctions can undergo activity-dependent modulation. Interestingly, single gap junctions show both voltage-dependent and -independent currents, which reflects multiple conductance sub-states of the junctional channel^{39–41}. Thus, gap junction opening and closing are graded rather than all-or-none.

Electrical coupling between cones

Electrical coupling between cone photoreceptors was first demonstrated in the turtle retina, where a current applied extrinsically to a cone produced activity in neighbouring (within 40 μm) cones⁴². The electrical coupling is derived from gap junctions formed between cones, a feature that is conserved across many species, including primates^{43–47} (Fig. 3). The gap junctions are found at the endings of fine processes — called telodendria — that emerge from the base of cone pedicles and contact adjacent cones. CX36 gap junction plaques are present here^{48–50}, but whether other connexins are incorporated in cone–cone gap junctions is unclear.

Recent studies have shown that the gap junctions between neighbouring mammalian cone photoreceptors have an effective conductance of a few hundred picosiemens, allowing for efficient transfer of visual signals^{51,52}. However, such lateral interaction between adjacent cones would be expected to introduce blurring of visual signals. Indeed, calculations indicate that electrical coupling between cones in the human fovea, where sampling is extremely dense, results in a blurring of visual signals and a reduction of acuity⁵¹. This calculated ‘neural blur’ due to cone coupling was subsequently confirmed by human psychophysical experiments⁵¹.

What, then, is the benefit of coupling between cone photoreceptors? Phototransduction is an inherently noisy process owing to random photon absorptions and fluctuations in signalling molecules and ion channel conductances in the signal processing cascade. The inherent noise in each cone is independent of that of its neighbours. By contrast, the vision-evoked activity of an individual cone is correlated with that of its neighbours owing to the reception of shared stimuli in a viewed image and the scattering of light as it passes through the cornea and lens. Coupling between cones sums the correlated visual signals and attenuates the asynchronous noise. It has been calculated that the coupling between foveal cones improves the signal-to-noise ratio of each cone by nearly 80%⁵¹. Overall, cone coupling improves the sensitivity and fidelity of visual signals, but at the cost of some neural blurring of the image. However, this neural blurring seems to be far narrower than the blurring produced by the optics of the eye⁵¹. Thus, the improvement in the signal-to-noise ratio of the cone signals outweighs the small degradation in acuity. An additional benefit of direct coupling between cones is that it removes noise before any distortions occur in the downstream retinal circuitry. Finally, psychophysical experiments do not detect any changes in neural blurring over a several-fold change in ambient illumination, suggesting that, in contrast to other retinal gap junctions (see below), those that couple cones are not affected by light⁵¹.

The retinas of humans and certain Old world monkeys contain three types of cone photoreceptors, which preferentially absorb long (red), medium (green) and short (blue) wavelengths of light⁵³. This trio of cone types underlies colour perception in the visual system. Although blue cones do not seem to have gap junctions, coupling between red and green cones is indiscriminate, in that green cones are coupled to green cones, red cones are coupled to red cones, and red cones are coupled to green cones^{50,54}. This indiscriminate coupling blurs the spectral discrimination between cones, as their signals partially mix.

However, this spectral blurring is modest, with colour discrimination reduced by only 20%⁵⁴. Further, red and green cones form regular but separate mosaics, resulting in a high probability of homologous coupling (between like cones) and a lower probability of heterologous coupling (between unlike cones) across the retina. This characteristic patchiness of red and green cone mosaics further minimizes the spectral blurring associated with electrical coupling⁵⁵.

Electrical coupling between rods and cones

In mammals, rod and cone photoreceptors make chemical synapses with different bipolar cells, segregating their signals into parallel retinal streams^{56,57}. Although more than ten subtypes of cone bipolar cells have been identified, only a single subtype of rod bipolar cell exists^{58,59}. This would seem to suggest that the rod circuitry in the retina is relatively simple, but it is now clear that multiple pathways transmit rod signals across the retina⁶⁰ (Fig. 4). In the primary rod pathway, rod photoreceptors pass signals to rod bipolar cells, which carry the signals radially to the inner retina and contact AII amacrine cells. The AII cells, in turn, form sign-inverting chemical synapses with OFF cone bipolar cell axons and sign-conserving electrical synapses with ON cone bipolar cell axons. Thus, the primary rod pathway ‘piggybacks’ onto the cone circuitry in the inner retina so that its signals can reach the output ganglion cells.

In addition, there are gap junctions between the axon terminals of rod and cone photoreceptors⁶¹ (Fig. 3). This rod–cone coupling provides an alternative, ‘secondary’ rod pathway for the transmission of scotopic signals (Fig. 4). In this pathway, rod signals are transmitted directly to cones, then to cone bipolar cells and then to ganglion cells. experimental evidence for the functionality of this pathway includes the detection of rod-generated signals in cone photoreceptors^{62,63} and the survival of rod signals in ganglion cells after blockade of the primary rod pathway^{64,65}. Human psychophysical studies support the existence of multiple rod pathways^{66–69}.

Physiological studies indicate that the functions of the two rod pathways relate to differences in the sensitivities of the signals that they carry as well as in the ganglion cells that they target. Studies using retinas from CX36-knockout mice, in which the rod–cone gap junctions are disrupted, indicate that the signals carried by the primary rod pathway are the most sensitive to stimulus brightness^{65,70}. By contrast, rod signals carried by the secondary pathway are approximately one log unit less sensitive. The two rod pathways thus have largely different operating ranges. Although the primary rod pathway has high sensitivity, its nonlinear synaptic transfer properties result in a narrow operating range⁷¹. The secondary rod pathway thus provides a route for scotopic signals to reach the ganglion cells when the primary pathway is saturated⁷².

A second difference between the primary and secondary rod pathways relates to the ganglion cell subtypes that they target. In rabbits the two pathways target different ganglion cell subtypes⁶⁴, whereas in mice they converge onto most of the OFF ganglion cells⁷³. A recent study⁶⁵ found both segregated and convergent signalling of the rod pathways to single ganglion cells. This indicates not only the complexity of the pathways by which rod signals are propagated in the retina, but also the complex organization of these signals’ transmission to central visual areas.

The conductance of the gap junctions between rod and cone photoreceptors is regulated by a circadian clock in the retina¹². In this scheme, the circadian clock increases dopamine release during the day, which activates D2/D4 dopamine receptors on rods and cones. This in turn lowers intracellular cAMP and protein kinase A (PKA) activity, which reduces the conductance of rod–cone gap junctions (Fig. 2). By contrast, reduced dopamine release at

night allows for robust electrical coupling between rods and cones. This circadian control ensures that the secondary rod pathway is operational in night time conditions, to facilitate the detection of dim objects. Further, the reduction of rod–cone coupling during the day ensures that cone signals are not passed to a saturated — and thus non-operational — network of rods, which would attenuate the signals created in bright conditions.

Electrical coupling between rods

The contribution of rod–cone gap junctions to a secondary rod pathway was challenged by a study of mice that were genetically engineered to lack cone photoreceptors⁷³. In these animals, rod responses in OFF ganglion cells occurred even when the primary rod pathway was blocked. As the mice had no rod–cone gap junctions, it was suggested that the alternative rod pathway is subserved by direct chemical synapses between rods and OFF bipolar cells rather than by rod–cone gap junctions. Although such contacts were thought not to exist in mammals^{45,56,74}, subsequent studies described them in a number of species^{47,75–77}.

Indeed, there is now functional evidence that direct chemical synapses between rods and OFF bipolar cells form a third rod pathway in the mammalian retina⁶⁵ (Figs 3,4). Interestingly, only one in five rods in the mouse retina forms a chemical synapse with an OFF bipolar cell, suggesting that this pathway may play a relatively limited part in scotopic signal transmission⁴⁷. However, gap junctions exist between the axon terminals of mammalian rod photoreceptors, including those of primates^{47,52}. It has been proposed that rod–rod coupling pools the scotopic signals at the photoreceptor level for conveyance to the ganglion cells through the third pathway. This third rod pathway might thus be useful at dusk and dawn, when more photons are available than during starlight, and the pooled signal might thereby efficiently encode faintly backlit objects⁴⁷.

Physiological evidence for this third pathway includes the finding of rod signals in ganglion cells after disruption of the primary and secondary rod pathways⁶⁵. Further, these signals showed scotopic sensitivities that were lower than those conveyed by the other two rod pathways, supporting the hypothesis that the third rod pathway subserves rod vision during dusk and dawn. The suggestion that the third rod pathway has a unique function is further supported by the finding that most of the ganglion cells targeted by this pathway do not receive input from the other two rod pathways⁶⁵. Interestingly, the signals that are transmitted by the third rod pathway survive in the CX36-knockout mouse retina, in which both AII–bipolar cell and rod–cone gap junctions are disrupted, suggesting that pooling of signals by rod–rod coupling is intact in these mice⁶⁵ and that CX36 is not expressed by rod photoreceptors.

Electrical coupling of horizontal cells

Horizontal cells are second-order retinal neurons that extend processes laterally in the outer plexiform layer, where they contact both rod and cone photoreceptors⁷⁸. In fact, Yamada and Ishikawa⁷⁹ first described “fused membrane structures” between neighbouring horizontal cells ~5 years before Goodenough and Revel³ coined the term gap junction. Subsequently, there have been numerous demonstrations of coupling between horizontal cells using dyes and tracers^{16,80–83} (Fig. 3).

The extensive gap junctional coupling between horizontal cells results in their characteristically large receptive fields, which can be 25 times the size of an individual cell's dendritic arbor^{81,84,85}. This indicates an extremely efficient lateral spread of visual signals through electrical synapses⁸¹. Indeed, the deletion of horizontal cell gap junctions in the

retina of CX57 (also known as GJA10)-knockout mice⁸⁶ resulted in a significant reduction in the cells' receptive field sizes⁸⁷.

Bipolar cells, the radially projecting second-order neurons in the retina, have antagonistic centre-surround receptive fields. This results in light-evoked responses that signal the difference in illuminance of an attended object (the centre) and that of the background environment (the surround)^{88,89}. Bipolar cells are thus contrast detectors. There is considerable evidence that the large receptive fields of horizontal cells provide the surround receptive field of bipolar cells and the output ganglion cells^{90–93}. It remains unclear whether bipolar cell surrounds are created by direct inhibitory horizontal cell synapses onto bipolar cells or by feedback inhibitory synapses of horizontal cells onto cone photoreceptors. To some controversy, it has been suggested that the feedback inhibition is not chemical, but ephaptic, and that electrical charge thus moves across horizontal cell hemichannels into the extracellular space to modify the activity of cone photoreceptors⁹⁴. Regardless of the above, horizontal cell coupling serves to form a homogeneous electrical syncytium by which a signal of the average ambient background illuminance is created. In essence, gap junctional coupling between horizontal cells is thought to form the initial mechanism for contrast detection in the visual system, although this idea has recently been challenged⁹⁵.

There are now converging sources of evidence that horizontal cell coupling is under dynamic regulation. For example, dopamine decreases the gap junctional conductance of horizontal cells and, acting through the intracellular messenger cAMP, produces a concomitant reduction in receptive field size^{22,96,97} (Fig. 2). Dopamine modifies gap junctional conductance by affecting junctional densities and/or mean open conductance times^{98–101}. Nitric oxide also alters the electrical coupling of horizontal cells, acting through the intracellular messenger cGMP^{19,102–104} (Fig 2). In rabbits, exposure to either dopamine¹⁰⁵ or the nitric oxide substrate L-arginine¹⁰⁶ reduces electrical coupling between horizontal cells.

Both the extracellular levels of dopamine and the production and release of nitric oxide are modulated by changes in illuminance, suggesting that horizontal cell coupling can be modulated by light^{17,107–110}. Indeed, both prolonged darkness and light adaptation have been shown to uncouple horizontal cells in a number of vertebrate retinas^{10,24,25,111–113}. There is a complex triphasic relationship between the conductance of horizontal cell gap junctions and illuminance, whereby coupling is poor under both dark- and light-adapted conditions and strong only under intermediate illuminance levels^{10,25}.

As expected, light-induced changes in horizontal cell coupling affect the centre-surround receptive field organization of retinal neurons and contrast signalling. Prolonged darkness attenuates the surround receptive fields of ganglion cells, which is thought to increase sensitivity at dim light at the expense of contrast detection^{114–116}. likewise, a reduction of horizontal cell coupling under bright light results in smaller surround receptive fields and thus more local contrast detection, which is consistent with higher acuity. Overall, the light-induced modulation of horizontal cell coupling optimizes the extraction of important cues in natural images, including contrasts and edges^{117,118}.

All amacrine cell gap junctions

Rod bipolar cells do not make contacts directly with ganglion cells, but instead form synapses with the intermediary AII amacrine cells (Figs 3,4). These AII cells express two types of gap junctions: neighbouring AII cells form gap junctions with one another and with the axon terminals of cone bipolar cells^{45,119,120}. As described earlier, these latter contacts form a conduit for rod signals to use the cone pathways before reaching the output ganglion cells.

Plaques of CX36 are found at dendritic crossings of AII cells, suggesting that AII–AII gap junctions are homotypic^{70,121}. However, both CX36 and CX45 are expressed at cone bipolar cell hemichannels, indicating that at least some of the AII cell–cone bipolar cell gap junctions might be heterotypic^{70,121–125}, although the existence of CX45–CX36 heterotypic junctions has been questioned¹²⁶. Such variations in composition could explain the different conductances and pharmacologies of AII–AII and AII cell–cone bipolar cell gap junctions^{127,128}.

AII cell–cone bipolar cell gap junctions

Deletion of CX36 disrupts both the AII–bipolar cell and the rod–cone gap junctions, resulting in the loss of signalling in the primary and secondary rod pathways, respectively^{65,70,129}. As a result, all rod-driven input to ON ganglion cells is lost. These results not only show that electrical synapses play an essential part in the rod pathways, but also provide the first demonstration that gap junctions are obligatory elements in a defined circuit in the CNS.

Paired recordings indicate that the AII–cone bipolar cell gap junctions can pass current bidirectionally¹²⁸: rod signals are passed from AII amacrine cells to cone bipolar cells under dark-adapted conditions, but there is a reversal in the direction of signal flow under light-adapted conditions and, as a result, cone signals move into the network of coupled AII cells¹³⁰. The conductances of the AII–cone bipolar cell gap junctions are modulated by nitric oxide acting through a cGMP cascade^{8,23} (Fig. 2). However, no light-induced changes in the conductances of these gap junctions have yet been found⁸.

AII–AII amacrine cell gap junctions

Based on computational models, Smith and vardi¹³¹ speculated that AII–AII cell coupling serves to sum synchronous signals and subtract asynchronous noise, thereby preserving the high sensitivity of signals carried by the primary rod pathway. Consistent with this idea, the intensity response profiles of the most sensitive ganglion cells in the retina show a rightward shift when electrical synapses between AII amacrine cells are deleted in CX36-knockout mice⁶⁵. AII–AII cell coupling thus underlies a unique function of the primary rod pathway: maintaining the high sensitivity of rod signals arriving in the inner retina.

The dendrites of the dopaminergic subtype of amacrine cell form a dense plexus that surrounds the AII amacrine cells¹³², and dopamine modulates the conductance of AII–AII cell gap junctions through a cAMP-mediated PKA cascade^{21,127,133,134} (Fig. 2). As dopamine release is modulated by light¹⁶, it is not surprising that changes in light adaptation are found to affect the coupling between AII amacrine cells in a triphasic manner, as described earlier for horizontal cells⁸ (Fig. 5). Thus, dark-adapted AII cells are coupled in relatively small groups and show relatively small receptive fields, but exposure to dim background light increases both parameters approximately sevenfold¹³⁰. Further light adaptation brings about a decrease in coupling to levels similar to those seen in dark-adapted retinas. These robust concomitant changes in tracer coupling and receptive field size of AII cells indicate a clear modulation of AII–AII cell coupling under different adaptational states.

The light-induced changes in AII–AII cell coupling enable these cells, as vital elements in the rod pathway, to remain responsive throughout the entire scotopic and mesopic range²⁶. In this scheme (Fig. 5), dark adaptation is analogous to starlight conditions, under which rods only sporadically absorb photons of light. Accordingly, the AII cells are relatively uncoupled in the sense that the few correlated signals are carried by only closely neighbouring AII cells; extensive coupling would dissipate signals into a largely inactive network, thereby attenuating them. Presentation of dim background light, analogous to

twilight conditions, brings about a greater than tenfold increase in AII cell coupling. This increased coupling allows summation of synchronous activity over a wider network of active AII cells, thereby preserving signal fidelity. This transition in coupling suggests that there are two basic operating states for AII cells under scotopic or mesopic light conditions: first, the ability to respond to single photon events; and second, summing signals over a relatively large area to augment synchronized events above the background noise.

Electrical coupling between ganglion cells

Possibly the most complex electrical synaptic networks occur in the inner retina, where most ganglion cell subtypes show gap junction-mediated tracer coupling with neighbouring ganglion and/or amacrine cells^{80,135–137} (Figs 3,6). Interestingly, coupling between different subtypes of ganglion cells has never been reported, suggesting that ganglion cell gap junctions subserve separate electrical networks in the inner retina.

At first glance, the extensive coupling displayed by ganglion cells seems counterintuitive, in that it suggests that there is lateral intercellular propagation of signals across the inner plexiform layer. This would result in a reduction of the visual acuity of neuronal signals just as they exit the retina. However, the receptive fields of ganglion cells approximate the extent of their dendritic arbors, irrespective of the extent of tracer coupling¹³⁸. This is because the conductance of ganglion cell gap junctions is low, which restricts the movement of both electrical current and tracers. Thus, ganglion cell gap junctions probably underlie local operations rather than the global processing that is exemplified by the extensive electrical syncytia formed by horizontal cells in the outer retina.

Beginning with the seminal work of mastronarde^{139–141}, a number of studies have shown that ganglion cell coupling underlies the coherent firing of neighbouring cells, ranging from broad correlations spanning several tens of milliseconds to finely tuned spike synchrony with 1–3ms latencies^{142–146}. This concerted firing accounts for up to one-half of retinal spike activity, suggesting that electrical coupling plays an important part in encoding visual information^{147,148}.

The homologous ganglion cell–ganglion cell and the heterologous ganglion cell–amacrine cell coupling that are found in the inner retina are thought to produce different patterns of concerted activity in neighbouring ganglion cells^{143–145} (Fig. 6). Direct ganglion cell–ganglion cell coupling is thought to mediate a fast (<2 ms) and reciprocal excitation that is reflected by prominent dual peaks in cross-correlograms of the spike activity of ganglion cell neighbours. By contrast, ganglion cells that are coupled indirectly through gap junctions with a common cohort of amacrine cells produce cross-correlograms with a narrow, unimodal contour. This latter correlation profile, which accounts for most of the concerted spike activity in the retina¹⁴⁸, probably reflects electrical synaptic inputs from common amacrine cells that give rise to synchronous spikes. Consistent with this idea, ganglion cell–amacrine cell coupling is the most common pattern of gap junctional coupling in the inner retina^{136,137}.

Correlated firing is thought to compress information for efficient transmission and thereby increase the bandwidth of the optic nerve¹⁴⁹. In this scheme, synchronous activity forms a separate stream of information to the brain, in addition to the asynchronous signals from individual ganglion cells. Concerted spike activity is also thought to enhance the saliency of visual signals by increasing the temporal summation at central targets^{150–152}. In this way, concerted ganglion cell activity might provide the temporal precision by which retinal signals are reliably transmitted to central targets¹⁵³.

The regulation of ganglion cell gap junctions is presently unclear. However, alpha ganglion cell coupling is dramatically increased under light-adapted conditions, resulting in an increase in concerted spike activity¹⁴⁵. Interestingly, this increase in coupling seems to be generated by a light-induced elevation of extracellular dopamine that binds to D2/D4 receptors (Fig. 2). It has been proposed that activated D2/D4 receptors initiate an intracellular cascade involving the attenuation of adenylyl cyclase activity, thereby inhibiting PKA and reducing phosphorylation of alpha ganglion cell connexins¹⁵⁴. The light-induced regulation of ganglion cell gap junction conductance is thus opposite to that described above for horizontal cell and for AII amacrine cell coupling^{10,130}.

Intercellular communication through gap junctions also plays an important part in the development of neuronal circuits, including cell differentiation and pathfinding^{155,156}. Gap junctions are thought to have a crucial role in regulating concerted ganglion cell activity in the developing retina, which is seen as spontaneous waves of depolarization^{157,158}. These spontaneous waves in turn are crucial to the refinement of retinal-thalamic and intraretinal connections^{157,158}.

ON direction-selective ganglion cells

As we described in the previous section, the general functional role of ganglion cell coupling is to synchronize the activities of neighbouring cells. A recent study of ON direction-selective (DS) ganglion cells revealed a specific role for synchronization of neighbouring cells in encoding the direction of stimulus motion¹⁵⁹. The DS ganglion cells are a unique subtype of ganglion cell that respond vigorously to stimulus movement in a preferred direction but weakly to movement in the opposite, or null, direction¹⁶⁰. The ON subtype of DS cells project to the accessory optic system^{161–163}, where their directional signals underlie the optokinetic response¹⁶⁴.

Neighbouring ON DS ganglion cells are coupled indirectly through gap junctions with a subtype of polyaxonal amacrine cell¹⁵⁹ (FIG. 7a) and show both correlated and synchronous activity in response to moving and stationary light stimuli. The correlated activity, which is reflected as a broad profile in the cross-correlogram, is unaffected by disruption of gap junctions, suggesting that it results from common inputs derived from the conventional excitatory chemical synapses between the ON DS ganglion cells and bipolar cells. By contrast, gap junction blockade eliminates synchronous spiking between ON DS cell neighbours, indicating that the synchronous spiking is due to electrical coupling. As described above, this type of ganglion cell spike synchrony is thought to result from indirect coupling to common amacrine cells. most interesting is the finding that the degree of spike synchrony between neighbouring ON DS cells was dramatically affected by the direction of stimulus movement¹⁵⁹ (Fig. 7b). Synchronized spiking was evoked by stimulus movement in all but the null direction, which produced a dramatic desynchronization of activity. Although previous studies have shown that changes in the state of dark–light adaptation can globally modulate the coupling between retinal neurons^{8,10,111}, this finding indicates that specific light stimulation can also effectively modulate the coupling between neurons to alter their response activity.

As described in the previous section, a number of global functions have been attributed to spike synchrony, including the enhanced saliency of visual signals or the increased temporal precision by which retinal signals are reliably transmitted to thalamic and cortical areas^{147,150,153}. By contrast, the synchronous spiking of neighbouring ON DS ganglion cells seems to have a more clearly defined and focused role, namely to encode the direction of stimulus motion. Interestingly, it is not the synchrony but the desynchronization to stimulus movement in the null direction that seems to be a key component of how ON DS cells signal

direction of movement. Overall, these results show that a dynamic modulation of the intercellular current transmitted through gap junctions forms a mechanism by which cell groups can encode specific information.

Conclusions and future directions

like at other CNS loci, it is now clear that electrical coupling through gap junctions is ubiquitous in the vertebrate retina. Gap junctions and their subunit connexin proteins are not only widely distributed in both synaptic layers, but converging evidence suggests that they are also expressed by most of the ~60 subtypes of retinal neurons. The finding that gap junctional conductances are affected by neuromodulators that mediate the changes in light adaptation and circadian rhythms indicates that electrical synaptic transmission forms a complex and dynamic mode of cellular communication. Despite the fact that we are just beginning to elucidate the types of connexins (and pannexins) that are expressed in the retina, it is already clear that gap junctions have a wide variety of functions in propagating and integrating signals. Unlike studies carried out in other parts of the CNS that often assign generic functions to electrical coupling, such as increased spike synchrony, studies in the retina have been able to detail the specific roles of individual gap junctions in visual processing. This makes the retina arguably the best model system in which to study the roles of electrical synaptic transmission in the CNS.

One way to determine the function of a gap junction is to remove it, and so pharmacological blockers and connexin-knockout mice have become important resources for studying the roles of electrical synaptic transmission in the brain. Future studies using more selective genetic formulations such as cell-specific and inducible connexin-knockout mouse models will accelerate our understanding of the contribution of particular retinal gap junctions to visual signalling. As we learn more about the properties that distinguish the different connexins, it will be important to determine the link between these properties, such as voltage and neuromodulator sensitivity, and the function of the particular gap junctions in which the different connexins are expressed.

Defects in gap junctions have been linked to a number of neurological pathologies in both the CNS and the PNS¹⁶⁵. Thus, developing a further understanding of the regulation of gap junctions, as well as the dynamic relationship between electrical and chemical transmission, is an important challenge for the future. There is no doubt that future studies will reveal new and crucial roles for gap junctions in neural processing and that the retina will remain a vital resource in this endeavour.

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Glossary

Amacrine cell	An interneuron located in the inner plexiform layer of the retina, at the level where bipolar cells and ganglion cells synapse.
Gap junction plaque	A collection of up to thousands of single gap junction channels.
Bipolar cell	A cell that receives information formed by the interactions of horizontal cells with cone or rod photoreceptors and conveys it to the inner retina. ON (cone or rod) bipolar cells respond to increases in intensity, whereas OFF cone bipolar cells respond to decreases in intensity.
AII amacrine cell	A subtype of retinal amacrine cell with a small dendritic field that conveys the rod signal to cone bipolar cells.
Sign-inverting synapse	A synapse that inverts the polarity of the signal passed from the pre- to the postsynaptic neuron.
Sign-conserving synapse	A synapse that preserves the polarity of the signal passed from the pre- to the postsynaptic neuron.
Ganglion cells	The output neurons of the retina, the axons of which form the optic nerve. ON ganglion cells respond to increases in light intensity, whereas OFF ganglion cells respond to decreases in light intensity.
Scotopic	Relating to dim ambient light conditions under which only rod photoreceptors are active.
Horizontal cells	Retinal neurons that form a network just beneath the photoreceptors that is responsible for averaging visual activity over space and time, which is important for contrast signalling.
Receptive field	A dynamic area of the retina in which stimulus presentation leads to the response of a particular cell.
Ephaptic	Relating to the direct electrical interaction between neighbouring neurons, mediated by current flow through the extracellular space that separates them.
Mesopic	Relating to the ambient light condition under which both rod and cone photoreceptors are active.
Accessory optic system	A visuosensory pathway with a direct retinal input to the midbrain.

Optokinetic response

A compensatory eye movement that stabilizes an image on the retina during slow head rotation.

Pannexins

Proteins expressed in both vertebrates and invertebrates that can form intercellular gap junction channels. They are genetically related to the invertebrate innexin family but are not related to connexins.

Figure 1. Structure and molecular organization of gap junctions

a | Gap junctions are formed between the opposing membranes of neighbouring cells. Hemichannels on each side dock to one another to form conductive channels between the two cells. An extended field of these channels forms a gap junctional plaque. Each hemichannel, or connexon, is comprised of 6 connexin protein subunits that are oriented perpendicular to the cells' membranes to form a central pore. This central pore serves as a conduit for ions and low-molecular-mass molecules of up to 1,000 Da. Connexons can contain only one type of connexin subunit (homomeric connexons) or a mixture of different connexins (heteromeric connexons). Gap junctional channels can consist of two of the same connexon (homotypic channels) or of connexons with different subunit compositions (heterotypic channels). **b** | Connexin subunits are proteins that have four transmembrane domains, two extracellular loops (E1 and E2) and one intracellular loop, as well as carboxyl and amino termini in the cytoplasm. Although the four transmembrane domains (M1–M4) share a conservative sequence that is important for docking in the cellular membrane, their cytoplasmic domains vary in length and amino acid sequence. Regulation of the three-dimensional connexin structure, which underlies the opening and closing of gap junction channels, is mediated at the cytoplasmic regions.

Figure 2. Neuromodulators affect gap junction conductances through intracellular pathways
 A summary of the intracellular pathways by which dopamine (DA) and nitric oxide (NO) are thought to affect the conductance of retinal gap junctions. DA release from dopaminergic amacrine cells is increased by light. For some retinal neurons DA binds to D1 receptors (left panel), activating adenylate cyclase (ACy) and increasing the concentration of cyclic AMP. This in turn activates cAMP-dependent protein kinase (PKA), the phosphorylation of connexins and a reduction in the conductance (g) of gap junctions. (However, it has recently been suggested that in AII amacrine cells PKA activates a phosphatase (Ph) that dephosphorylates connexins and thereby causes reduced gap junction conductance²¹) This D1 receptor mechanism occurs at gap junctions between horizontal cells (HC-HC)^{18,19}, between AII amacrine cells (AII-AII)^{21,23,134}, between other amacrine cell subtypes (AC-AC)¹⁵⁴ and at the amacrine cell hemichannel of amacrine cell-ganglion cell gap junctions (AC-GC)¹⁵⁴. DA also binds to D2/4 receptors (middle panel), which reduces the activity of adenylate cyclase, resulting in a reduction of cAMP levels. This reduces the activity of PKA, resulting in increased gap junction conductance. This mechanism occurs at gap junctions between rods and cones (R-C)¹², between ganglion cells (GC-GC)¹⁵⁴ and at the ganglion cell hemichannel of ganglion cell-amacrine cell gap

junctions (GC–AC)¹⁵⁴. Light also increases the release of NO from NADPH/nitric oxide synthase (NOS)-positive amacrine cells (right panel). NO diffuses into retinal neurons and activates guanylate cyclase (GCy), resulting in an increase in cGMP levels, activation of a cGMP-dependent protein kinase (PKG), phosphorylation of connexins and reduced gap junction conductance. This mechanism occurs at gap junctions between horizontal cells (HC–HC)^{11,103,104} and between AII amacrine cells and ON cone bipolar cells (AII–CB)²³.

Figure 3. Gap junctions expressed by retinal neurons

This schematic shows seven examples of electrical coupling, the different functions of which are detailed in the main text. The coloured ovals represent gap junction hemichannels. The solid and dotted arrows represent excitatory and inhibitory chemical synapses, respectively. **a** | Both hemichannels of the gap junctions that couple neighbouring cones (C) express CX36 (Refs 48,49). **b** | In rod (R)–cone gap junctions, only the hemichannel on the cone side contains CX36; the connexin on the rod side remains unknown^{48,49,65,70}. **c** | The type of connexin in rod–rod gap junctions is also unknown. **d** | Horizontal cell (HC) dendrites are extensively coupled. In mammals, axonless horizontal cells express CX50 (Ref. 166) whereas axon-bearing horizontal cells express CX57 (Refs 86,87). **e,f** | AII amacrine cells (AII) form two types of gap junction. Gap junctions between AII cells seem to be homotypic and comprised of homomeric hemichannels containing CX36 (**e**)^{70,121,122}. By contrast, gap junctions between AII amacrine cells and ON cone bipolar cells (CB) can be homotypic or heterotypic, with the AII cell hemichannels containing CX36 and the cone bipolar cell hemichannel containing either CX36 or CX45 (Refs 70,121–125). **g** | Ganglion cells (GC) are extensively coupled to each other and/or to neighbouring amacrine cells (AC). To date, ganglion cell gap junctions have been reported to contain CX36 or CX45 (Refs 167–169). GCL; ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; ONL, outer nuclear layer; OPL, outer plexiform layer; RB, rod bipolar cell.

Figure 4. The three rod pathways in the mammalian retina

a | The primary rod pathway involves electrical synapses between AII amacrine cells (AII), and between AII cells and cone bipolar cells (CB). In this pathway, signals are transmitted from rods (R) to rod bipolar cells (RB) and subsequently to AII cells. AII cells make sign-conserving electrical synapses with ON cone bipolar cells and sign-inverting inhibitory chemical synapses with OFF cone bipolar cells. In turn, the ON and OFF cone bipolar cells make excitatory chemical synapses with ON and OFF ganglion cells (GC), respectively. **b** | The secondary rod pathway involves electrical synapses between rod and cone photoreceptors (C). In this pathway, rod signals are transmitted directly from rods to cone photoreceptors through interconnecting gap junctions. The rod signals are then relayed to ON and OFF cone bipolar cells, which carry the signals to ganglion cells in the inner retina. **c** | The tertiary rod pathway involves electrical synapses between rods only. In this pathway, rods make direct chemical synapses with a subset of OFF bipolar cells (BC), which transmit the signals to some OFF ganglion cells. This pathway does not seem to have a counterpart in the ON circuitry. The solid and dotted arrows represent excitatory and inhibitory chemical synapses, respectively. Figure is modified, with permission, from Ref. 65 © (2006) Society for Neuroscience.

Figure 5. Electrical coupling between AII amacrine cells is regulated by background light conditions

The extent of coupling between AII amacrine cells under three different background light conditions, mimicking starlight, twilight and daylight³⁴. Each group of red symbols provides the average extent of Neurobiotin tracer coupling of rabbit AII amacrine cells. Under dim starlight conditions, the conductance of the gap junctions connecting neighbouring AII amacrine cells is relatively low, and so tracer movement is limited to only a few cells. As the ambient background light increases to twilight conditions, the conductance of the gap junctions increases and so the electrical syncytium of the coupled cells enlarges dramatically. Under bright daylight conditions, the conductance of the gap junctions is once again reduced and electrical communication is limited to a small group of cells. This triphasic modulation of AII cell coupling to light is similar to that seen for horizontal cells and ensures that the fidelity of the signals carried by the primary rod pathway is maintained under different scotopic conditions¹⁵². Under bright background conditions, the limited coupling between AII amacrine cells limits lateral interactions that would blur the image, thereby maintaining the high acuity that is essential for daylight vision¹⁴⁴. Figure is modified, with permission, from Ref. 26 © (2004) Elsevier.

Figure 6. Ganglion cell gap junctions underlie two patterns of concerted spike activity
a | Direct electrical coupling between neighbouring ganglion cells (GC) (left panel, red and brown) results in concerted activity. Paired recordings from coupled ganglion cell neighbours generate a cross-correlogram function with a distinct pattern consisting of two peaks with short latencies of approximately 1–3 ms (right panel). These two peaks reflect reciprocal interactions in which a spike in one cell gives rise to a spike in a coupled neighbour. **b** | Indirect electrical coupling between ganglion cells (red and brown) through gap junctions with a mutual intermediary amacrine cell (AC) (blue) (left panel) results in synchronous activity. Paired recordings from neighbouring ganglion cells give rise to a cross-correlogram with a peak at time 0, indicative of extensive synchronous spike activity (right panel). This pattern of synchrony reflects spiking in an amacrine cell producing spike activity in neighbouring ganglion cells with identical temporal properties.

Figure 7. Synchronous activity of coupled ON direction-selective ganglion cells encodes the direction of moving light stimuli

a | An ON direction-selective (DS) ganglion cell (GC) in the rabbit retina labelled with Neurobiotin. This ganglion cell is coupled to an array of polyaxonal amacrine cells (AC), the somata of which lie in the inner nuclear layer and are thus out of focus. However, the dendritic and axonal processes of the coupled polyaxonal amacrine cells are well labelled. **b** | An illustration of simultaneous extracellular recordings from two neighbouring ON DS ganglion cells, showing the responses to a rectangular slit of light moving in the preferred (top panels) and opposite (null) (bottom panels) directions. When the stimulus moves in the preferred direction, most of the light-evoked spikes are synchronized (red). By contrast, the movement in the opposite, null direction results in a complete loss of spike synchrony. The modulation of synchronous activity can be visualized in the cross-correlogram functions of the simultaneous paired recordings. When the slit is moved in the preferred direction the correlogram shows a large peak at time 0, corresponding to synchronized spiking. However, the peak is lost when the stimulus is moved in the null direction. The change in spike synchrony is due to a modulation of the intercellular current that flows through gap junctions between ON DS ganglion cells and polyaxonal amacrine cells. The change in response synchrony modifies the summation of the signal at central targets in the accessory optic system, thereby signalling the direction of stimulus motion to the brain. Figure is modified, with permission, from Ref. 159 © (2006) Society for Neuroscience.