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The ever-changing electrical synapse

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Abstract

A wealth of research has revealed that electrical synapses in the central nervous system exhibit a high degree of plasticity. Several recent studies, particularly in the retina and inferior olive, highlight this plasticity. Three classes of mechanisms can alter electrical coupling over time courses ranging from milliseconds to days. Changes of membrane conductance through synaptic input or spiking activity shunt current and decouple neurons on the millisecond time scale. Such activity can also alter coupling symmetry, rectifying electrical synapses. More stable rectification can be accomplished through molecular asymmetry of the synapse itself. On the minutes time scale, changes in connexin phosphorylation can change coupling quasi-stably with order of magnitude dynamic range. On the hours to days time scale, changes in expression level of connexins alter coupling through the course of circadian time, over developmental time, or in response to tissue injury. Combined, all of these mechanisms allow electrical coupling to be highly dynamic, changing in response to demands at the whole network level, in small portions of a network, or at the level of an individual synapse.

Introduction

Synaptic communication is the most fundamental property of a nervous system. The two dominant forms of synaptic communication, chemical and electrical, serve complementary functions and frequently interact to provide a rich diversity of capabilities. Essential to the ability of the nervous system to assimilate and respond to information from the environment is synaptic plasticity. While plasticity has long been considered the domain of chemical synapses, electrical synapses have proven also to show remarkable plasticity on several time scales, making critical contributions to sensory adaptation and learning. This article will review recent advances in understanding the molecular mechanisms of electrical synaptic plasticity in the vertebrate central nervous system, and will provide some examples of how this plasticity contributes to the functional output of neural systems.

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Electrical synaptic plasticity comes in three flavors

There are several mechanisms by which the strength of electrical coupling between two neurons can be changed. These can be distilled down to three groups of mechanisms: 1) those that alter membrane properties of the communicating cells, 2) those that change the conductance of the gap junction, and 3) those that change the expression level of connexins, the gap junction proteins. First, mechanisms that alter the membrane properties of the coupled cells can have a significant impact on electrical coupling. Opening of ion channels that reduce the membrane resistance of the coupled cells can impose transient decoupling. This was first demonstrated by Spira and Bennett [1] in neurons that control pharyngeal contraction in the sea slug *Navanax*. Such transient decoupling has an onset time of a few milliseconds and can last for several seconds. An interesting corollary of this form of shunting inhibition is that it can lead to electrical rectification if the input resistances of the coupled cells differ. This is often the case with the coupled G and M cells of *Navanax* pharyngeal ganglia [1], and is also the case for heterologous coupling between AII amacrine cells and On cone bipolar cells in the mammalian retina [2].

Membrane conductances are not exclusively inhibitory to electrical coupling. In the club endings of goldfish auditory nerve afferents that form mixed chemical/electrical synapses on Mauthner cells, subthreshold Na^+ currents amplify spikelets propagated antidromically through the electrical synapses [3]. The magnitude of the elicited Na^+ current depends non-linearly on the membrane potential of the afferent, so changes of just a few millivolts can dramatically alter the efficacy of antidromic spike propagation. The presence of subthreshold Na^+ currents and differences in input resistance between the Mauthner cell and the club endings result in a strong asymmetry in coupling coefficients (the fraction of input voltage transmitted to the follower cell: V_2/V_1) for prodromic and antidromic spike propagation, favoring antidromic propagation. This electrical rectification is reinforced by molecular asymmetry in the gap junction, with Connexin 35 (Cx35), the closest fish homolog of mammalian Cx36, on the presynaptic (club ending) side and the closely related Cx34.7 on the postsynaptic side [••4]. The molecular asymmetry accounts for about 4-fold rectification in favor of antidromic current flow from the Mauthner cell to the club endings; differences in membrane properties amplify that to an average of more than 20-fold. The rectification of current flow supports a form of lateral excitation among the numerous auditory afferents, which are not directly electrically coupled, favoring their synchronized firing [••4].

Changes in the connexin protein itself can potently alter coupling. In gap junctions made of Cx36, the connexin forming the majority of electrical synapses in the vertebrate central nervous system, the magnitude of tracer transfer and electrical coupling are directly regulated by phosphorylation of the connexin [5,6]. This can be seen in the strong correlation between the diffusion coefficients for tracer through networks of coupled neurons and the phosphorylation state of Cx36 (Figure 1) [••7,••8]. The phosphorylation-driven changes in tracer coupling cover an order of magnitude change in diffusion coefficient, producing a large dynamic range for plasticity. Changes in tracer coupling in neurons have been correlated to indices of electrical coupling such as receptive field diameter in retinal AII amacrine cells [9] and intercellular electrical conductance in inferior

olive neurons [••10], indicating that changes in tracer coupling correspond to real changes in electrical coupling. Tracer coupling, by its nature, reports a system-level average of the functional states of the participating gap junctions. Within a single cell, the phosphorylation states of individual gap junctions are highly variable [••7,•11], with gap junctions well under one micron apart being in vastly different phosphorylation states. This reveals that the functional state is controlled at the level of the individual synapse, and suggests that the dynamic range for plasticity of individual electrical synapses is likely larger than the order of magnitude average value.

The biophysical basis for phosphorylation-driven changes in coupling strength has not been established. While phosphorylation has been found to change the relative prevalence of different subconductance states for several connexins [12–15], there is no evidence that it does so for Cx36. Instead, it is more likely that phosphorylation increases the number or open probability of functional channels in a gap junction. In gap junctions, it is understood that only a small fraction of channels present are functional, with estimates ranging from about 10% [16] to as low as 0.1% [17]. Changes in this parameter provide large latitude for plasticity, easily encompassing the order of magnitude dynamic range observed for phosphorylation-dependent plasticity.

Changes in connexin phosphorylation can occur on a seconds to minutes time scale and achieve quasi-stable states that depend on the activities of protein kinases and phosphatases that regulate it. This represents an intrinsic capability for intermediate-term plasticity that is a fundamental property of all electrical synapses composed of Cx36. Indeed, electrical synaptic plasticity driven by signaling pathways that control protein kinase or phosphatase activity is also well known in neurons that employ connexins other than Cx36. Retinal horizontal cells, which express Cx57 or Cx50 in mammals and several homologous connexins in fish, display strong regulation of coupling by protein kinase A signaling pathways [18]. The strong similarity to plasticity mechanisms in Cx36 electrical synapses suggests that such plasticity is a common feature of electrical synapses.

Finally, changes in expression level of connexins forming electrical synapses can influence coupling on a time scale of hours to weeks. Katti et al. [•19] observed circadian regulation of Cx36 transcript and protein level in mouse retina. Cx36 was elevated at night only in the photoreceptor synaptic layer, consistent with the time period when photoreceptor coupling is enhanced [••8,20,••21]. Profound changes in neuronal coupling during development are well known (reviewed in [22]). Park et al. [••23] have found recently that activation of group II metabotropic glutamate receptors drives the developmental increase in Cx36 expression in rodent hypothalamus and cortex via both transcriptional and translational mechanisms. $GABA_A$ receptor activation has the opposite effect. The interplay of these two signaling mechanisms plays a key role in shaping the stereotyped elevation of neuronal coupling in early postnatal development and gradual decline at later ages.

Transient increases in neuronal coupling are also observed following various forms of neuronal injury. Wang et al. [•24] found that group II mGluR activation is responsible for the pathological increase in coupling and Cx36 expression that occurs within 2 hours of ischemic injury, although only the translational mechanism played a role in this time

window. $GABA_A$ receptor activity played only an indirect role to reduce coupling by reducing excessive excitatory activity. Curiously, a recent study found that 24 hours of sleep deprivation in rats caused a reduction in Cx36 expression in the hypothalamus that persisted even after sleep recovery [25]. These findings suggest that even relatively mild stress can induce changes in coupling, although the significance of those changes is not fully understood at this time.

Seeing all of the light

Sensory systems are tasked with detecting and encoding huge dynamic ranges of stimulus intensity. The retina encounters a billion-fold range of light intensity daily, sending useful information to higher centers of the visual system throughout that range. A wide variety of adaptation mechanisms enable it to do so, and electrical synaptic plasticity plays a prominent role in tuning sensitivity of some circuits and in rewiring circuits during the transition from nighttime to daytime vision. The most complete understandings of the molecular mechanisms that control electrical synaptic plasticity have been developed in retinal neurons in recent years, revealing that mechanisms of plasticity are cell type specific but built around the core mechanisms discussed above.

Vertebrate photoreceptors are coupled both homologously (rod-rod and cone-cone) and heterologously (rod-cone), serving important functions to suppress voltage noise and shunt rod signals into the cone pathway, expanding the rod pathway dynamic range at its upper end. Coupling is reduced and rod input effectively eliminated from the cone pathway by adaptation to bright light and by a circadian mechanism during the subjective day [••21]. Li and colleagues have elucidated the signaling pathways that control these changes (Figure 2). Li et al. [•11] found that protein kinase A-mediated phosphorylation of Cx36 is responsible for supporting coupling, and that regulation of PKA activity is the central control point. In keeping with an extensive retinal literature, activation of dopamine D4 receptors in the daytime was found to reduce PKA activity and suppress coupling [••8]. However, Li et al. also found that nighttime activation of adenosine A2a receptors drove PKA activity and coupling up [••8]. The opposing actions of the Gi-coupled D4 receptor and the Gs-coupled A2a receptor, regulating adenylyl cyclase and consequently PKA activity, allow the photoreceptors to respond to extracellular cues that have opposite phases (dopamine: high in the day, low at night; adenosine: high at night, low in the day) [26]. Li et al. further found that transcript levels of D4 receptor, A2a receptor, and adenylyl cyclase isoform AC1 all varied rhythmically [••8], suggesting that changes in receptor abundance over the course of the day change the magnitude and relative efficacy of responses to the external cues. As a final twist, Li et al. [•27] have recently found in zebrafish retina that the adenosine A1 receptor, a Gi-coupled receptor with higher affinity for adenosine than A2a, actually uses the low daytime level of extracellular adenosine to reinforce the dopamine signal, keeping coupling low. The tight interplay of several G-protein coupled receptors allows photoreceptor coupling to be controlled with precision and high dynamic range by extracellular cues.

In the mammalian rod pathway, the AII amacrine cell is a central lynchpin neuron. It is the sole recipient of excitatory input from the rod bipolar cells of the primary rod pathway, and

through synaptic convergence from rod bipolar cells and receptive field expansion via extensive electrical coupling with its neighbors, sets the ultimate sensitivity limit of the retina. The excitatory output of the AII amacrine cell is obligately routed through electrical synapses with On cone bipolar cells, which in turn make excitatory synapses onto the On subset of retinal output neurons, the ganglion cells. These electrical synapses also provide the only known daytime function of the AII amacrine cell, to provide glycinergic inhibition of the Off pathway driven by On bipolar cell signals [•28].

The AII amacrine cell undergoes well-known and prominent changes in electrical coupling driven by light adaptation [9] that contribute to rewiring retinal circuitry from rod pathway dominated during dim light conditions to cone pathway dominated during bright light conditions. Kothmann and colleagues have recently identified the mechanisms that control this plasticity (Figure 3). The AII amacrine cell is characteristically poorly coupled in prolonged, complete darkness, but develops extensive coupling with dim background light [9]. Kothmann et al. [••29] found that this light-dependent enhancement in coupling is driven by glutamate spillover from On bipolar cell (either rod- or cone-driven) activity. Enhancement of coupling depends on activation of non-synaptic NMDA receptors, activation of CaM Kinase II, and phosphorylation of Cx36. The NMDA receptors involved do not contribute to the synaptic responses of AII amacrine cells to rod bipolar cells, but instead are co-localized with the gap junctions and are apparently present for the sole purpose of regulating electrical synaptic conductance. This activity-dependent potentiation of electrical synapses is very similar to that in the goldfish Mauthner cell [30], in which Ca^{2+} influx through synaptic NMDA receptors drives CaMKII activity, presumably phosphorylating the connexin present.

In the presence of bright light, AII amacrine cell coupling is reduced again in response to dopamine secretion and activation of dopamine D1 or D1-like receptors. Kothmann et al. [••7] found that activation of D1-like receptors reduced Cx36 phosphorylation. The Gs signaling of D1 receptors and their close relatives activates adenylyl cyclase and enhances PKA activity. Kothmann et al. [••7] found that PKA activity indeed drove *de-phosphorylation* of Cx36, and did so by activating protein phosphatase 2A. The AII amacrine cell thus differed from photoreceptors in that PKA activity had a negative impact on Cx36 phosphorylation and coupling. The signaling pathway in which PKA activates PP2A to dephosphorylate targets is replicated in non-neuronal cultured cells as well as other neurons, suggesting that this is a signaling module that is commonly used. The independent signaling pathways for phosphorylation and de-phosphorylation of the connexin that Kothmann described in AII amacrine cells are activated at different light intensity thresholds, imparting a biphasic pattern of electrical synaptic plasticity.

Among the many channels of information encoded by the retina, object motion is truly critical to life, as its detection can make the difference between catching prey and becoming prey. Trenholm and colleagues [•31] have found that electrical coupling among the dorsally coding On-Off directionally-selective ganglion cells imparts the remarkable ability to encode the leading edge of a stimulus at the same spatial location regardless of the speed of stimulus motion. This lag normalization depends on the transmission of a subthreshold excitatory receptive field surround through the electrical synapses to reinforce sparse

synaptic input from distant stimuli within the classical receptive field center [••32]. This lateral priming does not result in back-propagation of excitation after the trailing edge of the stimulus passes, which would result in stretching of the coded object. The skewed distribution of inhibitory input toward the null direction, which is critical for establishing direction selectivity and could produce shunting inhibition, does not particularly account for this phenomenon. Instead, currents associated with spiking activity of the cell create a transient refractory state that reduces electrical synaptic efficacy and transiently rectifies electrical synaptic transmission [••32]. The result is an effective system to encode object motion over a wide range of speeds without resulting in runaway excitation in the network.

Timing is everything

The olivo-cerebellar system is thought to provide timing signals to coordinate motor tasks and to provide timing information for non-motor and cognitive tasks [33]. Spontaneous subthreshold 5–10 Hz membrane potential oscillations in inferior olive (IO) neurons are thought to be the basis of this timing signal, entraining their sparse spike output. IO neurons are richly endowed with electrical synapses that can synchronize these oscillations, although coupling among IO neurons is typically weak. This can be useful in that, in the presence of strong excitatory input, moderately weak coupling can lead to chaotic desynchronization of subthreshold oscillations [34]. This increases the information content of the timing signals at the system level and enhances timing precision. The concept of adaptive coupling [•35] has been introduced to explain how motor learning can be accomplished by gradual reduction of coupling strength in appropriate pools of IO neurons to induce chaotic resonance and increase precision of the timing signal.

Several recent studies have revealed mechanisms through which IO coupling is controlled adaptively at a variety of time scales (Figure 4). Turecek et al. [••10] found that NMDA receptor activation, either through bath application of NMDA or through high-frequency stimulation of excitatory input to the IO, strengthened coupling over the course of several minutes. This effect required activation of CaMKII and was limited to weakly coupled IO neurons. Turecek et al. [••10] further found that non-synaptic NMDA receptors were closely associated with Cx36 gap junctions in the IO glomeruli, implicating a signaling pathway highly analogous to that of retinal AII amacrine cells [••29]. NMDA application induced synchrony and enhanced the amplitudes of subthreshold oscillations, revealing a mechanism by which excitatory input can enhance the synchrony of the IO network [••10].

In contrast to the findings of Turecek et al. [••10], Mathy et al. [••36] describe a mechanism through which excitatory input *depresses* IO coupling. Low frequency (1 Hz) stimulation of the excitatory input to the IO reduced coupling over the course of several minutes. This reduction in coupling depended on NMDA receptors, intracellular Ca^{2+}, and CaMKII activity [••36]. A potentially similar form of long-term depression of electrical synapses has been described in the thalamic reticular nucleus [37]. Coupling among IO neurons has been found to be highly variable [38], and the NMDA receptor-dependent mechanisms described by Mathy et al. [••36] and Turecek et al. [••10] can explain how local excitatory input can tune coupling strength in a manner analogous to the delicate balance between long-term potentiation and long-term depression in central glutamatergic synapses.

Finally, Lefler et al. [••39] have recently examined the mechanism through which GABAergic projections from the deep cerebellar nuclei (DCN) transiently decouple IO neurons. The arrangement of IO dendritic spines in glomeruli containing electrical synapses surrounded by inhibitory and excitatory terminals (Figure 4) prompted Llinas to propose 40 years ago that synaptic activation could transiently decouple IO neurons through shunting inhibition [40]. Lefler et al. [••39] tested this hypothesis using optogenetic stimulation of GABAergic neurons from the DCN that project to the IO. Light pulses produced inhibitory currents in IO neurons with slow time courses, which merged into steady sustained inhibitory currents during trains of pulses. This is in keeping with the recent finding that transmitter release from DCN neurons is largely asynchronous [•41], resulting in slow, sustained inhibition. The activation of GABAergic inhibitory currents reduced coupling coefficients between pairs of IO neurons and generally changed the coupling symmetry as well for time courses of a few hundreds of milliseconds. Single pulses of DCN activation altered the subthreshold oscillations of IO neurons, often shifting their phase, while trains of pulses eliminated subthreshold oscillations altogether. The oscillations recovered after pulse trains ended, implying that coupling within the IO network was necessary to sustain the oscillations. This bonanza of recent studies shows well how synaptic input tunes the network of IO neurons, with excitatory input adjusting coupling strength stably to set an optimal state to support timing signals via subthreshold oscillations, and inhibitory input transiently decoupling portions of the network to isolate their activity from that of their neighbors.

Concluding remarks

Electrical synapses have often been thought to represent simple and static elements of neural circuitry. The recent wealth of studies has highlighted the fact that they are highly dynamic and revealed a variety of mechanisms that change electrical coupling over time courses varying from milliseconds to days. The picture that has emerged is of synapses that can be constantly tuned to meet the needs of their specific circuit. Such plasticity is not a unique feature of the few electrical synapses discussed in this review, but should be considered a general feature of all electrical synapses. Indeed it is likely that electrical synaptic plasticity works alongside with chemical synaptic plasticity in most nervous system processes.

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References

1. Spira ME, Bennett MV. Synaptic control of electrotonic coupling between neurons. Brain Res. 1972; 37:294–300. http://dx.doi.org/10.1016/0006-8993(72)90674-9. [PubMed: 4334355]
2. Veruki ML, Hartveit E. Electrical synapses mediate signal transmission in the rod pathway of the mammalian retina. J Neurosci. 2002; 22:10558–10566. [PubMed: 12486148]
3. Curti S, Pereda AE. Voltage-dependent enhancement of electrical coupling by a subthreshold sodium current. J Neurosci. 2004; 24:3999–4010. http://dx.doi.org/10.1523/JNEUROSCI.0077-04.2004. [PubMed: 15102915]
••4. Rash JE, Curti S, Vanderpool KG, Kamasawa N, Nannapaneni S, Palacios-Prado N, Flores CE, Yasumura T, O'Brien J, Lynn BD, et al. Molecular and functional asymmetry at a vertebrate

electrical synapse. Neuron. 2013; 79:957–969. http://dx.doi.org/10.1016/j.neuron.2013.06.037This paper shows that electrical synapses at sensory afferent to Mauthner neuron mixed synapses in the reticulo-spinal system are asymmetric, containing Cx35 on the presynaptic side and Cx34.7 on the postsynaptic side. This asymmetry contributes to electrical rectification of signals passing through this synapse, and is the first evidence of a molecular basis for such rectification in the vertebrate central nervous system. [PubMed: 24012008]

5. Ouyang X, Winbow VM, Patel LS, Burr GS, Mitchell CK, O'Brien J. Protein kinase A mediates regulation of gap junctions containing connexin35 through a complex pathway. Brain Res Mol Brain Res. 2005; 135:1–11. http://dx.doi.org/10.1016/j.molbrainres.2004.10.045. [PubMed: 15857663]
6. Del Corsso, C.; Iglesias, R.; Zoidl, G.; Dermietzel, R.; Spray, DC. Calmodulin dependent protein kinase increases conductance at gap junctions formed by the neuronal gap junction protein connexin36. Brain Res. 2012. http://dx.doi.org/10.1016/j.brainres.2012.06.058
••7. Kothmann WW, Massey SC, O'Brien J. Dopamine-stimulated dephosphorylation of connexin 36 mediates AII amacrine cell uncoupling. J Neurosci. 2009; 29:14903–14911. http://dx.doi.org/10.1523/JNEUROSCI.3436-09.2009Kothmann et al. used phospho-Cx36 specific antibodies to show for the first time how coupling at an electrical synapse is controlled by protein kinase signaling and that the functional state of electrical synapses is controlled at the level of each individual synapse. The study showed a positive dependence of coupling on connexin phosphorylation, with a 20-fold dynamic range, and dispelled a decades-old misconception that gap junction phosphorylation reduced coupling. [PubMed: 19940186]
••8. Li H, Zhang Z, Blackburn MR, Wang SW, Ribelayga CP, O'Brien J. Adenosine and Dopamine Receptors Coregulate Photoreceptor Coupling via Gap Junction Phosphorylation in Mouse Retina. J Neurosci. 2013; 33:3135–3150. http://dx.doi.org/10.1523/JNEUROSCI.2807-12.2013This study showed for the first time that coupling among mammalian photoreceptors is controlled by a balance of signaling by opposing G-protein coupled receptors. This signaling uses extracellular adenosine as a nightime cue and dopamine as a daytime cue. Receptors for both are regulated cyclically through the day. [PubMed: 23407968]
9. Bloomfield SA, Volgyi B. Function and plasticity of homologous coupling between AII amacrine cells. Vision Res. 2004; 44:3297–3306. http://dx.doi.org/10.1016/j.visres.2004.07.012. [PubMed: 15535997]
••10. Turecek J, Yuen GS, Han VZ, Zeng XH, Bayer KU, Welsh JP. NMDA Receptor Activation Strengthens Weak Electrical Coupling in Mammalian Brain. Neuron. 2014; 81:1375–1388. http://dx.doi.org/10.1016/j.neuron.2014.01.024This paper showed for the first time a mechanism that enhanced coupling at inferior olive electrical synapses. The enhancement of coupling depended on strong activation of excitatory input and used an NMDA receptor-dependent mechanism analagous to that in Mauthner neurons and AII amacrine cells. [PubMed: 24656255]
•11. Li H, Chuang AZ, O'Brien J. Photoreceptor coupling is controlled by connexin 35 phosphorylation in zebrafish retina. J Neurosci. 2009; 29:15178–15186. http://dx.doi.org/10.1523/JNEUROSCI.3517-09.2009Li et al. showed for the fist time that prominent light-driven changes in photoreceptor coupling depend on phosphorylation of Cx36 and protein kinase A activity. [PubMed: 19955370]
12. Moreno AP, Saez JC, Fishman GI, Spray DC. Human connexin43 gap junction channels. Regulation of unitary conductances by phosphorylation. Circ Res. 1994; 74:1050–1057. Modulation review rev1.docx. [PubMed: 7514508]
13. Kwak BR, Hermans MM, De Jonge HR, Lohmann SM, Jongsma HJ, Chanson M. Differential regulation of distinct types of gap junction channels by similar phosphorylating conditions. Mol Biol Cell. 1995; 6:1707–1719. http://dx.doi.org/10.1091/mbc.6.12.1707. [PubMed: 8590800]
14. van Rijen HV, van Veen TA, Hermans MM, Jongsma HJ. Human connexin40 gap junction channels are modulated by cAMP. Cardiovasc Res. 2000; 45:941–951. http://dx.doi.org/10.1016/S0008-6363(99)00373-9. [PubMed: 10728420]
15. Ek-Vitorin JF, King TJ, Heyman NS, Lampe PD, Burt JM. Selectivity of connexin 43 channels is regulated through protein kinase C-dependent phosphorylation. Circ Res. 2006; 98:1498–1505. http://dx.doi.org/10.1161/01.RES.0000227572.45891.2c. [PubMed: 16709897]

16. Bukauskas FF, Jordan K, Bukauskiene A, Bennett MV, Lampe PD, Laird DW, Verselis VK. Clustering of connexin 43-enhanced green fluorescent protein gap junction channels and functional coupling in living cells. Proc Natl Acad Sci U S A. 2000; 97:2556–2561. http://dx.doi.org/10.1073/pnas.050588497. [PubMed: 10706639]

17. Curti S, Hoge G, Nagy JI, Pereda AE. Electrical Transmission between Mammalian Neurons is Supported by a Small Fraction of Gap Junction Channels. J Membr Biol. 2012; 245:283–290. http://dx.doi.org/10.1007/s00232-012-9449-z. [PubMed: 22729690]

18. Bloomfield SA, Volgyi B. The diverse functional roles and regulation of neuronal gap junctions in the retina. Nat Rev Neurosci. 2009; 10:495–506. http://dx.doi.org/10.1038/nrn2636. [PubMed: 19491906]

•19. Katti C, Butler R, Sekaran S. Diurnal and circadian regulation of connexin 36 transcript and protein in the mammalian retina. Invest Ophthalmol Vis Sci. 2013; 54:821–829. http://dx.doi.org/10.1167/iovs.12-10375Katti et al. showed that levels of Cx36 transcript and protein varied during the day in mouse retina, with higher levels at night and lower in the daytime. The rhythm of Cx36 protein depended on intact melatonin signaling, while the rhythm of Cx36 transcript was controlled in a circadian manner that did not require melatonin signaling. The changes in Cx36 protein may contribute to the nocturnal increase in photoreceptor coupling. [PubMed: 23307963]

20. Ribelayga C, Mangel SC. Identification of a circadian clock-controlled neural pathway in the rabbit retina. PLoS One. 2010; 5:e11020. http://dx.doi.org/10.1371/journal.pone.0011020. [PubMed: 20548772]

••21. Ribelayga C, Cao Y, Mangel SC. The circadian clock in the retina controls rod-cone coupling. Neuron. 2008; 59:790–801. http://dx.doi.org/10.1016/j.neuron.2008.07.017Ribelayga et al. showed that the extent of rod-cone coupling in the retina is controlled dramatically by a circadian rhythm, using a pathway that required D2-like dopamine receptors. This rhythm acts as a switch to allow cones to receive rod signals at night, but not in the daytime. [PubMed: 18786362]

22. Belousov AB, Fontes JD. Neuronal gap junctions: making and breaking connections during development and injury. Trends Neurosci. 2013; 36:227–236. http://dx.doi.org/10.1016/j.tins.2012.11.001. [PubMed: 23237660]

••23. Park WM, Wang Y, Park S, Denisova JV, Fontes JD, Belousov AB. Interplay of chemical neurotransmitters regulates developmental increase in electrical synapses. J Neurosci. 2011; 31:5909–5920. http://dx.doi.org/10.1523/JNEUROSCI.6787-10.2011Park et al. identified a number of mechanisms that control the developmental upregulation and subsequent downregulation of electrical synapses in the brain. Group II metabotropic glutamate receptor signaling, via cAMP/PKA, drove the increase while $GABA_A$ receptor signaling, via Ca^{2+}/PKC, drove the decrease. [PubMed: 21508216]

•24. Wang Y, Song JH, Denisova JV, Park WM, Fontes JD, Belousov AB. Neuronal gap junction coupling is regulated by glutamate and plays critical role in cell death during neuronal injury. J Neurosci. 2012; 32:713–725. http://dx.doi.org/10.1523/JNEUROSCI.3872-11.2012This study showed that a variety of types of neuronal injury cause a transient increase in neuronal gap junction coupling, using mechanisms related to those that occur during development. This transient increase in coupling made neurons more susceptible to death following the injury, and Cx36 knockout or gap junction blockers substantially preserved neurons in the zone closely surrounding the injury. [PubMed: 22238107]

25. Franco-Perez J, Ballesteros-Zebadua P, Fernandez-Figueroa EA, Ruiz-Olmedo I, Reyes-Grajeda P, Paz C. Sleep deprivation and sleep recovery modifies connexin36 and connexin43 protein levels in rat brain. Neuroreport. 2012; 23:103–107. http://dx.doi.org/10.1097/WNR.0b013e32834e8fcb. [PubMed: 22158029]

26. Ribelayga C, Mangel SC. A circadian clock and light/dark adaptation differentially regulate adenosine in the mammalian retina. J Neurosci. 2005; 25:215–222. http://dx.doi.org/10.1523/JNEUROSCI.3138-04.2005. [PubMed: 15634784]

•27. Li, H.; Chuang, AZ.; O'Brien, J. Regulation of photoreceptor gap junction phosphorylation by adenosine in zebrafish retina; Visual Neuroscience. 2014. p. 1-7.FirstViewhttp://dx.doi.org/10.1017/S095252381300062XThis study showed that adenosine A1 receptors contribute to extracellular signaling that controls photoreceptor coupling. The high-affinity A1 receptors use the low daytime level of extracellular adenosine to reinforce the uncoupling imposed by

dopamine D4 receptors. At night, activation of the lower affinity adenosine A2a receptors has a much stronger effect than that of the A1, resulting in relatively high coupling

•28. Manookin MB, Beaudoin DL, Ernst ZR, Flagel LJ, Demb JB. Disinhibition combines with excitation to extend the operating range of the OFF visual pathway in daylight. J Neurosci. 2008; 28:4136–4150. http://dx.doi.org/10.1523/JNEUROSCI.4274-07.2008This study showed that the AII amacrine cell, a canonical rod pathway neuron, has a daytime function as well. While relatively uncoupled from other AII amacrine cells in the daytime, electrical coupling with cone On bipolar cells sends signals through the AII amacrine cell to deliver glycinergic inhibition to the cone Off pathway. This enhances contrast in the visual scene. [PubMed: 18417693]

••29. Kothmann WW, Trexler EB, Whitaker CM, Li W, Massey SC, O'Brien J. Nonsynaptic NMDA Receptors Mediate Activity-Dependent Plasticity of Gap Junctional Coupling in the AII Amacrine Cell Network. J Neurosci. 2012; 32:6747–6759. http://dx.doi.org/10.1523/JNEUROSCI.5087-11.2012This study showed for the first time in a mammalian neuron that activity-dependent processes can potentiate an electrical synapse in a manner analagous to long-term potentiation at central glutamatergic synapses. The mechanism required NMDA receptors and Ca^{2+}/CaMKII signaling much as in glutamatergic chemical synapses. [PubMed: 22593045]

30. Pereda AE, Bell TD, Chang BH, Czernik AJ, Nairn AC, Soderling TR, Faber DS. Ca2+/calmodulin-dependent kinase II mediates simultaneous enhancement of gap-junctional conductance and glutamatergic transmission. Proc Natl Acad Sci U S A. 1998; 95:13272–13277. http://dx.doi.org/10.1073/pnas.95.22.13272. [PubMed: 9789078]

•31. Trenholm S, Schwab DJ, Balasubramanian V, Awatramani GB. Lag normalization in an electrically coupled neural network. Nat Neurosci. 2013; 16:154–156. http://dx.doi.org/10.1038/nn.3308Trenholm et al. show that neural mechanisms dependent on electrical coupling in a network of motion-coding retinal ganglion cells work to enable the cells to code the leading edge of a moving object at nearly the same spatial location regardless of the speed with which the object moves. [PubMed: 23313908]

••32. Trenholm S, McLaughlin AJ, Schwab DJ, Awatramani GB. Dynamic tuning of electrical and chemical synaptic transmission in a network of motion coding retinal neurons. J Neurosci. 2013; 33:14927–14938. http://dx.doi.org/10.1523/JNEUROSCI.0808-13.2013In this study, Trenholm and colleagues expand on the previous study to show that the lag normalization requires transient modulation of electrical coupling strength. This is accomplished by a form of shunting inhibition dependent on the spiking activity of the motion-coding cell. [PubMed: 24027292]

33. Jacobson GA, Rokni D, Yarom Y. A model of the olivo-cerebellar system as a temporal pattern generator. Trends Neurosci. 2008; 31:617–625. http://dx.doi.org/10.1016/j.tins.2008.09.005. [PubMed: 18952303]

34. Schweighofer N, Lang EJ, Kawato M. Role of the olivo-cerebellar complex in motor learning and control. Front Neural Circuits. 2013; 7:94. http://dx.doi.org/10.3389/fncir.2013.00094. [PubMed: 23754983]

•35. Tokuda IT, Hoang H, Schweighofer N, Kawato M. Adaptive coupling of inferior olive neurons in cerebellar learning. Neural Netw. 2013; 47:42–50. http://dx.doi.org/10.1016/j.neunet.2012.12.006Tokuda et al. show that adaptive changes in electrical coupling of inferior olive neurons can contribute to cerebellar learning. This occurs when coupling that synchronizes subthreshold oscillations in IO neurons is adaptively reduced to a state that supports chaotic resonance, thereby increasing the information content and precision of timing signals sent from the IO to the cerebellum. [PubMed: 23337637]

••36. Mathy A, Clark BA, Hausser M. Synaptically induced long-term modulation of electrical coupling in the inferior olive. Neuron. 2014; 81:1290–1296. http://dx.doi.org/10.1016/j.neuron.2014.01.005Mathy et al. show that low-frequency excitatory synaptic input to IO neurons induces long-term depression of electrical synaptic coupling. This provides a mechanism to adaptively reduce coupling in the IO network, and is potentially an important component of cerebellar learning. [PubMed: 24656251]

37. Haas JS, Zavala B, Landisman CE. Activity-dependent long-term depression of electrical synapses. Science. 2011; 334:389–393. http://dx.doi.org/10.1126/science.1207502. [PubMed: 22021860]

38. Hoge GJ, Davidson KG, Yasumura T, Castillo PE, Rash JE, Pereda AE. The extent and strength of electrical coupling between inferior olivary neurons is heterogeneous. J Neurophysiol. 2011; 105:1089–1101. http://dx.doi.org/10.1152/jn.00789.2010. [PubMed: 21177999]

••39. Lefler Y, Yarom Y, Uusisaari MY. Cerebellar inhibitory input to the inferior olive decreases electrical coupling and blocks subthreshold oscillations. Neuron. 2014; 81:1389–1400. http://dx.doi.org/10.1016/j.neuron.2014.02.032Lefler et al. show with optogenetic tools that inhibitory input from deep cerebellar nuclei transiently reduces IO neuron electrical coupling on a millisecond time scale and supresses subthreshold oscillations. The study demonstrates how signals from the cerebellum can tune IO network activity and consequently regulate the precisely timed and potent excitatory signals from the IO climbing fibers to the cerebellar Purkinje neurons. [PubMed: 24656256]

40. Llinas R, Baker R, Sotelo C. Electrotonic coupling between neurons in cat inferior olive. J Neurophysiol. 1974; 37:560–571. [PubMed: 4827022]

•41. Best AR, Regehr WG. Inhibitory regulation of electrically coupled neurons in the inferior olive is mediated by asynchronous release of GABA. Neuron. 2009; 62:555–565. http://dx.doi.org/10.1016/j.neuron.2009.04.018Best and Regehr show that the GABAergic output of the deep cerebellar nuclei neurons onto IO neurons is mediated largely by asynchronous vesicle release. This unusual mode of vesicle release for a central synapse plays an important role in the transient uncoupling of IO neurons by DCN input. The asynchronous mode of release ensures that inhibitory currents persist for a few hundred milliseconds, suppressing IO coupling through shunting inhibition. [PubMed: 19477156]

Highlights

- Electrical synapses have a high degree of functional plasticity.
- Different mechanisms alter electrical coupling in milliseconds to days time domains.
- Steady-state changes depend largely on electrical synapse protein phosphorylation.
- Many neural network mechanisms rely upon electrical synaptic plasticity.

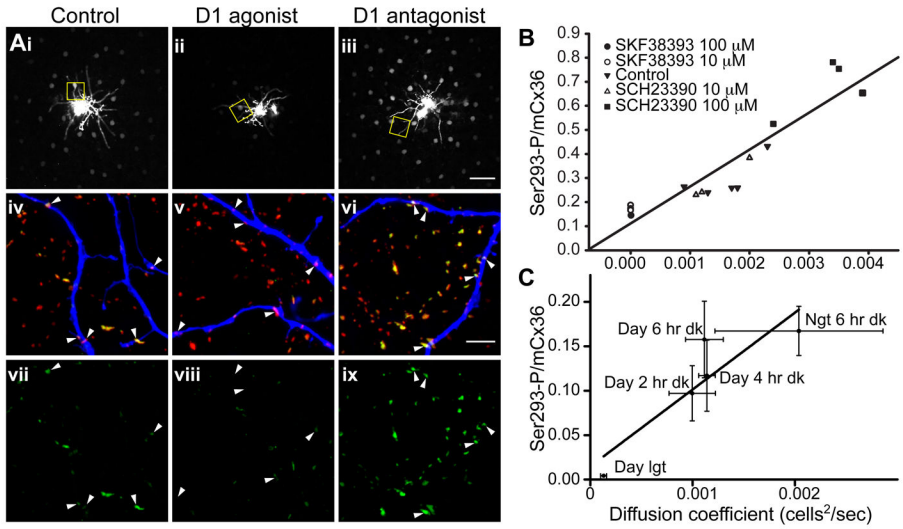

Figure 1.

Changes of tracer coupling in neurons correlate strongly with phosphorylation of Cx36. A) Neurobiotin injection into single AII amacrine cells in the rabbit retina results in filling arrays of cells (i–iii) by tracer diffusion through gap junctions. Tracer diffusion is reduced by application of dopamine D1 receptor agonist SKF38393 (ii) and increased by D1 receptor antagonist SCH23390 (iii). Immunostaining of the regions outlined with boxes in i–iii for total Cx36 (red channel) and Cx36-phospho-Ser293 (green channel) is shown in iv–vi; the blue channel shows Neurobiotin-filled dendrites of the injected cell. The phospho-Ser293 channel is shown alone in vii–ix. The D1 agonist reduces and D1 antagonist increases Cx36 phosphorylation. Arrowheads show gap junctions on the injected cell. B) Correlation between the average phosphorylation state of Cx36, defined as the ratio of phospho-S293 to total Cx36 on each Cx36 gap junction, and the diffusion coefficient for Neurobiotin derived by fitting tracer intensity data in somata of AII amacrine cells at various distances from the injected cell with a compartmental diffusion model. R^2 of the linear fit is 0.86. C) Similar correlation of data for photoreceptor coupling in C57Bl/6 mouse photoreceptors with parallel measurements of Cx36 phosphorylation. Animals were collected at night in darkness or in the day in light, or adapted to darkness for various times during the day. R^2 of linear fit to the data is 0.81. For both rabbit AII amacrine cells and mouse photoreceptors, the dynamic range for Neurobiotin diffusion coefficient was 20-fold. Panels A and B adapted from [••7]; Panel C adapted from [••8].

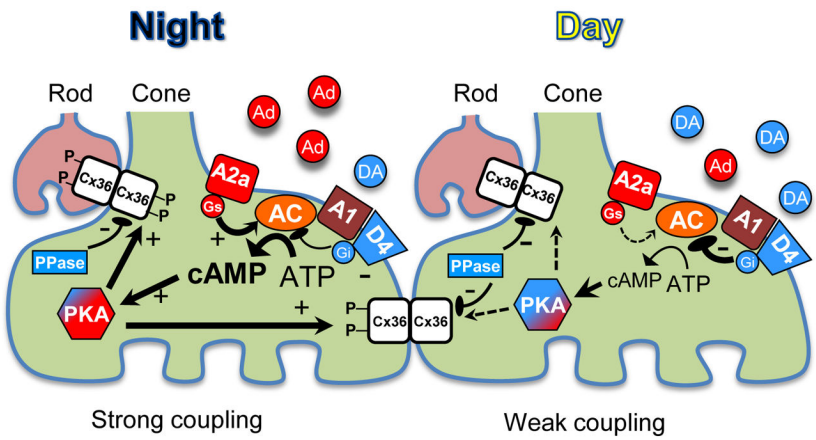

Figure 2.

Molecular mechanisms that control photoreceptor coupling. Changes in steady-state coupling are accomplished by altering the phosphorylation state of Cx36 through phosphorylation by PKA and dephosphorylation by a phosphatase. PKA activity is controlled dynamically through opposing G-protein signaling pathways that regulate adenylyl cyclase activity. These are in turn controlled by extracellular diffusible cues. At night (left side), extracellular adenosine (Ad) is relatively high and dopamine (DA) relatively low, favoring activation of adenosine A2a receptors and stimulation of adenylyl cyclase through Gs signaling. In the day (right side), extracellular dopamine is relatively high and adenosine relatively low, favoring activation of dopamine D4 receptors and adenosine A1 receptors. These both inhibit adenylyl cyclase through Gi signaling. The phosphatase is critical for regulation of coupling, but it is not currently known if its activity is constitutive or regulated.

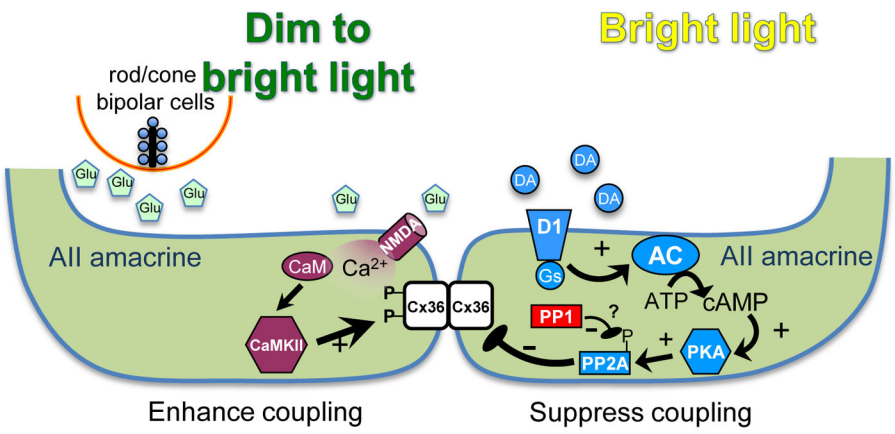

Figure 3.

Molecular mechanisms that control AII amacrine cell coupling. Changes in steady-state coupling are accomplished by opposing actions of an activity-dependent phosphorylating mechanism and a diffusible cue-dependent dephosphorylating mechanism. Non-synaptic NMDA receptors associated with the Cx36 gap junctions are activated by spillover glutamate derived from On pathway bipolar cells in response to any light (left side). NMDA receptor activation in turn activates CaMKII and phosphorylates Cx36 to enhance coupling. In the presence of bright light (right side), dopaminergic amacrine cells secrete dopamine, which activates D1 dopamine receptors on AII amacrine cells and many other targets. Gs signaling from D1 receptors activates adenylyl cyclase, increasing PKA activity. PKA activity in turn activates PP2A, which dephosphorylates Cx36 to reduce coupling. PP1 inhibits the pathway and is presumed to dephosphorylate PP2A. The light thresholds for these two pathways differ by several orders of magnitude, imparting a biphasic pattern of electrical coupling that adapts the AII amacrine cell to operate in different light regimes.

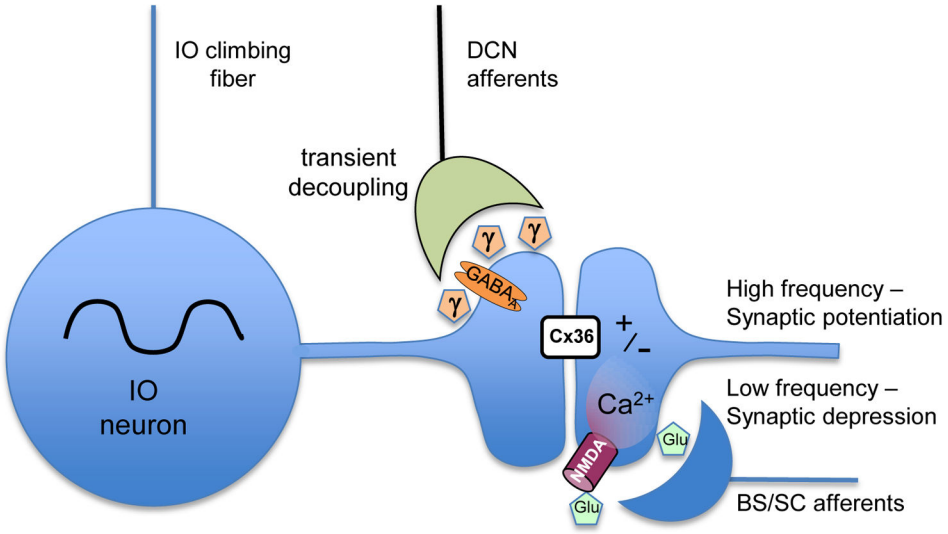

Figure 4.

Mechanisms that modulate coupling of Inferior Olive neurons on different time scales. IO neurons have electrical synapses on dendritic spines organized as glomeruli surrounded by GABAergic afferents descending from deep cerebellar nuclei (DCN) and glutamatergic afferents arising from brain stem and spinal chord neurons. Intrinsic subthreshold oscillations of IO neuron membrane potential are partially supported by electrical coupling. Activation of DCN neurons reduces and may rectify electrical coupling through shunting inhibition on a millisecond time scale. DCN input also suppresses subthreshold oscillations temporarily. High frequency stimulation of excitatory afferents from the brain stem and spinal chord (BS/SC afferents) increases steady-state coupling on a minutes time scale through a Ca^{2+} and CaMKII-dependent mechanism equivalent to that shown in figure 3. Conversely, low frequency stimulation of the excitatory afferents results in depression of steady-state coupling. This also occurs through a Ca^{2+} and CaMKII-dependent mechanism. This mechanism requires the activation of a phosphatase, but the details of this phosphatase activity are not yet known. The frequency-dependent modulation of coupling by excitatory afferents provides a mechanism to impose a learned code on the matrix of coupled IO neurons.