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TITLE: Synchrony and So Much More: Diverse Roles for Electrical Synapses in Neural Circuits

RUNNING TITLE: Diverse Roles for Electrical Synapses

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ABSTRACT

Electrical synapses are gap junctions between neurons that are ubiquitous across brain regions and species. The biophysical properties of most electrical synapses are relatively simple—transcellular channels allow nearly ohmic, bidirectional flow of ionic current. Yet these connections can play remarkably diverse roles when placed into different neural circuit contexts. Here I review recent findings illustrating how electrical synapses may excite or inhibit, synchronize or desynchronize, augment or diminish rhythms, phase-shift, detect coincidences, enhance signals relative to noise, adapt, and interact with nonlinear membrane and transmitter-release mechanisms. Most of these functions are likely to be widespread in central nervous systems.

KEY WORDS:

Electrical synapses

Gap junctions

Cx36

Synchrony

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INTRODUCTION

Electrical synapses—neuronal gap junctions—are ubiquitous components of vertebrate and invertebrate central nervous systems. Why?

A search for the answer can start with the appealing features of electrical synapses: impressive signaling speed, bidirectional communication (in most cases), functional and structural simplicity, energy efficiency, and an operating range that spans all physiological voltages (Bennett, 1997). These characteristics are fairly well conserved across the electrical synapses of all species and brain regions, at least compared to chemical synapses with their multiplicity of transmitters, receptors, release dynamics, and plasticity mechanisms. Perhaps electrical synapses are well adapted to some very particular, specialized, yet common function that all neural circuits require?

This seems unlikely, even if we consider only the early descriptions of electrical synapses. Strong, steeply rectifying connections in crayfish and hatchetfish suggested advantages of signaling speed, direction, and security (Furshpan and Potter, 1957, 1959; Auerbach and Bennett, 1969). Weaker, bidirectional electrotonic coupling in lobsters, fish, and cats implied roles for coordinating and synchronizing the activity of neural networks (Watanabe, 1958; Bennett et al., 1963; Llinas et al., 1974). Speed has been deemphasized in mammalian systems because the synaptic delays of chemical synapses at 37°C rival those of electrical synapses (Sabatini and Regehr, 1996), but synchrony has remained a broadly popular function for electrical synapses (Bennett and Zukin, 2004; Connors and Long, 2004).

The computational functions of electrical synapses are far richer than “speed and synchrony” imply, as Marder (1998) pointed out. Our understanding of these functions has multiplied as electrical synapses have been explored in more types of neurons and their circuits. Here I will examine some of the more recent findings, with a bias toward studies of vertebrate systems. I will not discuss the detailed structure and biophysics of gap junction channels, or the roles of electrical synapses in development, plasticity, or intercellular chemical signaling, which have been reviewed recently and elegantly (Elias and Kriegstein, 2008; Belousov and Fontes, 2013; O'Brien, 2014; Pereda, 2014; Palacios-Prado et al., 2014; Niculescu and Lohmann, 2014; Haas et al., 2016; Pereda, 2016; Skerritt and Williams, 2017). My goal is to review the eclectic functions of electrical junctions.

Electrical synapses can excite *and* inhibit

Electrical synapses heed Ohm’s Law: net ionic current will flow through the gap junction channels proportional to the transjunctional voltage (Bennett, 1977; Connors, 2009). Therefore, anything that depolarizes one neuron—action potentials, excitatory postsynaptic potentials (EPSPs), low-threshold calcium currents, for example—relative to its more quiescent neighboring cells can lead to transjunctional current that excites the neighbors.

Unlike chemical synapses, the large majority of electrical synapses conduct bidirectionally. This is especially true in vertebrate systems. If input patterns change and an active neuron suddenly becomes quiet while previously quiet neurons activate, current through the electrical synapses will reverse direction. Unlike most chemical synapses, electrical synapses are also analog;

spikes are not necessarily required for transmission, their signal is not quantized in vesicles, and the strength of their influence depends in a graded way on the transsynaptic voltage difference. [Single gap junction channels do have a gating mechanism that abruptly opens and closes them, so in this narrow sense electrical synaptic transmission is quantized by the currents through individual channels (Harris and Locke, 2009). However single-channel currents of neuronal gap junction channels are usually small, the number of channels in an electrical synapse is usually large, gap junction channels may have both voltage-sensitive and -insensitive states (Moreno et al., 1994), and voltage changes are low-pass filtered by local membrane properties, so in practice many electrical synapses operate in an effectively analog mode. A caveat: while the number of channels in a gap junction plaque is often large, this may be mitigated by the very small fraction—less than 1% —of channels that actually contribute to junctional conductance (Lin and Faber, 1988; Curti et al., 2012).] The upshot of bidirectional analog signaling is that electrical synapses allow a group of neurons to rapidly share and distribute excitation. This distribution can lead to interesting patterns of network activity, including synchrony, rhythms, and more.

Neurons can also inhibit with electrical synapses, in various ways. An obvious but potentially important way is when one or more cells generate inhibitory PSPs (IPSPs) from chemical synapses and transmit a fraction of the IPSP's hyperpolarization to neighbors through electrical synapses. A more subtle form of inhibition was succinctly described by Bennett (1977): "An important case…is provided by cells that are closely coupled electrically and are synchronized by electrotonic synapses (see below). In this situation the coupling synapses both excite and inhibit. A depolarized cell depolarizes its less depolarized neighbors and is simultaneously made less depolarized by them. Restated, if one cell is at a potential where it excites another cell, it is simultaneously inhibited by that other cell."

Another inhibitory mechanism occurs when an action potential (a decidedly excitatory event) in one neuron is transformed into a primarily inhibitory electrical PSP as it passes through an electrical synapse (Galarreta and Hestrin, 2001). Such a transformation works best with action potentials of a particular shape, namely a very brief depolarizing spike followed by a deep and much longer-lasting afterhyperpolarization (AHP). This kind of action potential is severely distorted as it is transmitted via electrical synapses because of low-pass filtering, i.e. high-frequency components of the action potential (the spike) are attenuated more than low-frequency components (the AHP) (Gibson et al., 2005). Filtering in this case is not due to any magical property of gap junction channel biophysics. It occurs because all cell membranes have considerable electrical capacitance and resistance, and that combination tends to slow the speed of all voltage changes by amounts dictated by the cells' membrane time constants (Rall, 1969; Bennett, 1977). The outcome for a quick spike-slow AHP waveform, as it passes from cell-to-cell via electrical synapses, is that the depolarizing spike shrinks considerably (to perhaps 1% of its presynaptic height, in a typical case), and is then called a "spikelet", while the AHP shrinks much less (to about 10%) (Connors, 2009). The electrotonically conducted AHP can then exert an inhibitory effect on the postsynaptic cell.

Electrically coupled neurons with quick spike-slow AHP waveforms are common in the mammalian CNS. Examples include the fast-spiking (FS) inhibitory interneurons of the neocortex, the inhibitory Golgi cells of the cerebellum, and the inhibitory Golgi cells of the

dorsal cochlear nucleus. And indeed, the electrical PSPs transmitted by cortical FS cells (Galarreta and Hestrin, 2001; Gibson et al., 2005) and both types of Golgi cells (Dugué et al., 2009; Yaeger and Trussell, 2016) have fast but tiny spikelets followed by relatively large, protracted hyperpolarizations when recorded *in vitro*. These biphasic electrical PSPs have sequential effects, first briefly (~2 msec) and modestly exciting and then more slowly (~50-100 msec) inhibiting. Electrically coupled neurons whose action potentials lack a deep AHP, such as the somatostatin-expressing interneurons of neocortex, transmit more purely monophasic, depolarizing electrical signals (Gibson et al., 2005). The precise shape of the electrical PSP can have important consequences for the spiking dynamics and synchrony of coupled networks (Pfeuty et al., 2003; Ostojic et al., 2009).

The strength and even the valence of electrical PSPs can change dramatically and dynamically as the membrane potentials of electrically coupled neurons fluctuate. This may happen during shifts of sleep-wake states, slow oscillations, or pathological processes. In a study of cortical FS interneurons (Otsuka and Kawaguchi, 2013), the cells' electrical PSPs generated strong inhibition when cells were in depolarized states (and AHPs were large). Electrical PSPs from the same cells were entirely depolarizing and excitatory, however, when membrane potentials were in more hyperpolarized states (and AHPs were very small). In Golgi cells of the cerebellum, electrically conducted spike AHPs can inhibit neighboring cells *in vitro* (Vervaeke et al., 2010). Recordings from Golgi cells in intact mice show, however, that the hyperpolarizing phase of the electrical PSP is considerably less prominent, and the PSP has a predominantly excitatory effect (van Welie et al., 2016). Perhaps state-dependent factors, including more depolarized membrane potentials, spontaneous synaptic fluctuations, and modulation of intrinsic ion channels, can regulate the valence of electrical synaptic communication.

Anything that triggers a hyperpolarization can, in principle, generate inhibition mediated by an electrical synapse. A novel example comes from neurons in the dorsal cochlear nucleus of mice, where stellate cells are electrically coupled to fusiform cells (Apostolides and Trussell, 2013). Glutamatergic synapses onto the fusiform cells can first trigger an EPSP and, secondarily, a protracted hyperpolarization mediated by the deactivation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (see below). A fraction of this intrinsically generated hyperpolarization in the fusiform cells is transferred to stellate cells via electrical synapses (Apostolides and Trussell, 2014).

Electrical synapses can mediate phase-locking, synchrony, and antisynchrony of action potentials

Many neurons are superb biological oscillators (Stiefel and Ermentrout, 2016). Synapses, including electrical synapses, can couple neuronal oscillators into interactive networks that generate simple or complex dynamics.

One widely documented function of electrical synapses, at least in networks of similar neurons coupled by nonrectifying gap junctions, is synchronization (Bennett and Zukin, 2004; Connors and Long, 2004). Synchrony, as defined here, means that the spike timing (or other fluctuations of membrane potentials) of two or more neurons coincide within some criterion of temporal precision. Electrical synapses can mediate strong and temporally precise (typically as small as

±1 msec, but perhaps <1 µsec in favorable neural systems) synchrony of both subthreshold membrane potentials and action potentials under the right conditions. As each neuron receives a synaptic input or generates an action potential, a small ionic current moves across its electrical synapses into or out of its neighboring neurons. These intercellular currents influence the neighbors' membrane potentials and bias their spiking probabilities slightly; spike timing, and thus phase compared to other neurons' spikes, can be advanced or delayed. The emergent dynamics of electrically coupled excitable cells depend on multiple factors: the sites and strengths of electrical synapses, the intrinsic physiology and heterogeneity of the participating neurons, the addition of chemical synaptic interconnections, the size of the networks, and the nature and strength of background drives. The mechanisms by which gap junctions can mediate synchronous activity have been explored in an extensive theoretical and modeling literature (e.g. Kepler et al., 1990; Sherman and Rinzel, 1992; Chow et al., 1998; White et al., 1998; Moortgat et al., 2000; Traub et al., 2001; Lewis and Rinzel, 2003; Pfeuty et al., 2003; Saraga et al., 2006; Ostojic et al., 2009; Lewis and Skinner, 2012).

The phenomenology of electrical synapse-mediated synchrony has been abundantly documented *in vitro*. Examples from vertebrates range across all levels of the central nervous system, and include a diverse array of neuron types, sizes, and roles, including: excitatory spinal motor neurons (Kiehn and Tresch, 2002; Personius et al., 2007), excitatory neurons of the inferior olive (Manor et al., 1997; Leznik et al., 2002; Long et al., 2002), inhibitory interneurons of the cerebellar cortex (Mann-Metzer and Yarom, 1999; Dugué et al., 2009; Vervaeke et al., 2010), inhibitory and excitatory neurons of the retina (Veruki and Hartveit, 2002; Trenholm et al., 2014), inhibitory neurons of the thalamic reticular nucleus (Landisman et al., 2002; Long et al., 2004), several types of inhibitory interneurons in the neocortex (Galarreta and Hestrin, 1999; Gibson et al., 1999; Beierlein et al., 2000; Deans et al., 2001; Blatow et al., 2003; Mancilla et al., 2007; Caputi et al., 2009; Hu and Agmon, 2015), and neurons of the suprachiasmatic nucleus (Colwell, 2000; Long et al., 2005). In general, the robustness of phase-locking and synchrony correlate well with the strength of electrical coupling. Electrically coupled networks become asynchronous when coupling strengths are weak or spiking rates are low (Chow and Kopell, 2000).

Demonstrations of synchronizing mechanisms in isolated preparations can be highly informative, and they allow detailed exploration of mechanisms, but ultimately they must be tested also *in vivo*. This has been a serious challenge to traditional methods. There have been very few attempts to directly measure the relationship between electrical synapses and synchrony in intact vertebrate brains. In an inspiring feat of electrophysiology, van Welie et al. (2016) recently described paired whole-cell recordings from cerebellar Golgi cells in anesthetized mice. Their data demonstrate, first, that Golgi cells *in vivo* are indeed electrically coupled, as *in vitro* work had suggested (Dugué et al., 2009); second, that electrical synapses *in vivo* can mediate spike synchrony with millisecond precision; and third, that synchrony depends on electrical synapses spreading both slow, subthreshold fluctuations across the Golgi network as well as fast, spike-triggered electrical PSPs. *In vivo,* precise phase-locking, including synchrony, occurred between spikes generated spontaneously or in response to natural sensory inputs (van Welie et al. (2016).

Dendritic electrical synapses are often not enough to induce temporally sharp spike synchrony, perhaps because of their weakness or locations distant from spike-generating zones (axon initial segments in many neurons) (Saraga et al., 2006; Lewis and Skinner, 2012; Schwemmer and Lewis, 2014). Active conductances in dendrites (Johnston and Narayan, 2008) may enhance or suppress the phase-locking effects of electrical synapses. For some neurons, a concerted drive from electrical and chemical synapses is required to achieve effective synchrony. Examples include mitral cells in the olfactory bulb (Christie et al., 2005), cerebellar Golgi cells (Vervaeke et al., 2012), retinal ganglion cells (Trenholm et al., 2014), and some systems of cortical inhibitory interneurons (Tamás et al., 2000; Hu and Agmon, 2015; Salkoff et al., 2015; Neske and Connors, 2016).

Synchrony is only one possible dynamic state of electrically coupled networks, and it is sometimes not the most stable state. In a pair of synchronous, electrically coupled neurons the phase of spikes can shift as one cell is driven more strongly than the other. If the cells remain phase-locked they are also necessarily frequency-locked, but the tendency for the more strongly driven cell to spike sooner than the second cell causes the spikes of the second to lag those of the first. Such phase-synchrony can break down into asynchrony when excitatory drives onto cell pairs, and their resulting intrinsic firing frequencies (i.e. their frequencies under the same conditions but in the absence of electrical coupling), diverge by more than about 10% (Mancilla et al., 2007). The stability of phase-locking correlates with coupling strength.

Interconnected neurons may also generate precise *anti*synchrony—alternating spikes or bursts in antiphase, i.e. with phase lags equal to half of the interspike interval. A traditional notion is that robust antisynchrony can emerge from pairs or groups of neurons that mutually inhibit one another, as in alternating locomotor circuits (Brown, 1914). Systems of model neurons with mutual inhibition can generate both synchrony and antisynchrony, sometimes bistably (Wang and Rinzel, 1992; van Vreeswijk et al., 1994; Lewis and Rinzel, 2003; Bem and Rinzel, 2004). Recordings from pairs of mutually inhibitory neurons in the cerebral cortex confirmed that they can generate antisynchronous and synchronous spiking, depending on conditions (Gibson et al., 2005; Merriam et al., 2005; Hu and Agmon, 2011).

Antisynchrony in neurons connected only by electrical synapses is predicted by some computational models (e.g. Sherman and Rinzel, 1992; Chow and Kopell, 2000; Nomura et al., 2003; Bem and Rinzel, 2004). This might seem counter-intuitive, but recall that electrical synapses can also mediate inhibition. In fact, antisynchrony among electrically coupled model neurons is particularly sensitive to the shapes of action potentials and the intrinsic membrane conductances that underlie them (Chow and Kopell, 2000; Pfeuty et al., 2003; Nomura et al., 2003). Antisynchronous states are often quite fragile, particularly as the sites of electrical synapses move more distally, away from spike-generating zones (Schwemmer and Lewis, 2014).

Alas, experimental attempts to demonstrate spike antisynchrony mediated by electrical synapses alone have been unsuccessful so far. Bem et al. (2005) studied pairs of snail neurons connected, using a dynamic clamp system, with simulated electrical and/or chemical synapses (in fact, the simultaneously recorded neurons were actually in different ganglion preparations). Bistable antisynchrony and synchrony were easily supported by inhibitory connections with the addition of some electrical coupling, but the investigators could not persuade their cells to fire

in antisynchrony when they were connected exclusively by electrical synapses. Gibson et al. (2005) and Mancilla et al. (2007) studied cortical interneurons that were connected by natural chemical inhibitory and/or electrical synapses. Inhibition alone supported either synchrony or antisynchrony, depending on spike frequency; the presence of electrical synapses in addition to inhibition tended to stabilize the synchronous state, but cells coupled only by electrical synapses would not support antisychrony. Merriam et al. (2005) also recorded from cortical interneurons, used dynamic clamp to connect them, and concluded that electrical coupling by itself could not mediate antisynchrony.

Many of the experimental studies reviewed here were performed on minimal neural circuits: cell pairs. Larger coupled networks are more realistic, complex, and poorly understood. The brain itself is a network of networks. Remarkably, in the special case of chimera states, some large nonbiological networks of coupled oscillators (mechanical metronomes!) can generate synchrony and disorder simultaneously (Blaha et al., 2016). Chimera states have been explored in simulated systems of large neural networks (Omelchenko et al., 2015; Bera et al., 2016; Majhi et al., 2016) but not yet, to my knowledge, in any real biological systems.

Electrical synapses can trigger *de*synchronization

Another remarkable phenomenon of an electrical coupled network is rapid switching from spike synchrony to a transient state of desynchronization. This has been demonstrated most clearly in local networks of inhibitory Golgi interneurons in the cerebellar cortex *in vitro* (Vervaeke et al., 2010). Golgi cells are interconnected primarily by electrical synapses of varying strengths. Because their action potentials have a deep, slow AHP, their electrical PSPs include a strong inhibitory phase, as described above (Dugué et al., 2009). Under resting states the Golgi cells spike rhythmically and, thanks to their electrical synapses, quite synchronously. However, when one or more cells are abruptly excited by a synaptic input strong enough to trigger an action potential, inhibitory (hyperpolarizing) electrical PSPs of varying strengths and durations propagate out into neighboring cells. These heterogeneous electrical PSPs induce different shifts in the timing of spikes among the local Golgi cells, effectively desynchronizing them. In the absence of further excitatory inputs the network slowly, over seconds, resynchronizes and resumes its synchronous rhythmicity. Thus, depending on recent history, the same electrical synapses within the Golgi cell network can mediate *either* synchrony and transient desynchrony of its spiking.

The key properties required for electrical synapse-mediated desynchronization—action potentials with deep AHPs, electrical synapses of assorted strength, strong and sparse excitatory inputs—are common in the brain, so this mechanism may be widespread (Connors et al., 2010).

Electrical synapses may facilitate or even induce network rhythmicity

Many single neurons can generate intrinsic periodic activity, or rhythms. As we saw above, electrical synapses can synchronize or otherwise coordinate rhythms within a network of neurons. But can electrical synapses actually induce rhythms in a network of neurons that are otherwise nonrhythmic? Perhaps. The inferior olive provides a case study.

The excitatory cells of the inferior olivary nucleus are a well-studied system of gap junction-coupled neurons. Their axons project to the cerebellar cortex and form the powerful climbing fiber inputs to Purkinje cells. Olivary neurons have a curious electrophysiology; they express strong voltage-dependent calcium and other conductances in their dendrites, and these allow them to generate spontaneous, robust, usually subthreshold oscillations of about 5-15 Hz, as well as unusually broad action potentials (Crill, 1970; Llinas and Yarom, 1981; Benardo and Foster, 1986; Mathy et al., 2009). Olivary cells are directly interconnected by electrical synapses only (Sotelo et al., 1974; Llinas, 2013). Not surprisingly, this coupling can synchronize their subthreshold voltage fluctuations as well as occasional action potentials that are phase-locked to subthreshold cycles (Leznik et al., 2002; Long et al., 2002; De Zeeuw et al., 2003; Leznik and Llinás, 2005).

Electrical coupling between olivary cells requires connexin36 (Cx36), the primary neuronal gap junction protein. Deletion of the Cx36-coding gene effectively abolishes electrical coupling between olivary neurons (Long et al., 2002; De Zeeuw et al., 2003). Under these conditions, the large majority of synaptically disconnected neurons continue to generate spontaneous oscillations, albeit asynchronously. The simplest explanation is that most individual olivary neurons are vigorous oscillators under normal, wild-type conditions, and that electrical synapses allow neighboring cells to synchronize their rhythms (Long et al., 2002). An alternative possibility originates from computational models showing that, in principle, subthreshold rhythms themselves could be an emergent property of electrically coupled networks of intrinsically *non*rhythmic cells (Smolen et al., 1993; Manor et al., 1997; Loewenstein et al., 2001). Inferior olivary versions of the models employ simulated neurons with olive-like, though heterogeneous, combinations of active membrane properties, coupled by electrical synapses. In the absence of coupling and external drives, the neurons are silent and rest at different membrane potentials; adequately strong electrical coupling allows their potentials to begin equalizing, bringing them into a voltage range compatible with spontaneous or conditional rhythmicity.

The hypothesis that rhythmicity per se—not just the synchrony of rhythms—depends on electrical synapses in the olive has yet to be tested directly. Genetic deletion of Cx36 suffers from potential uncontrolled complications of developmental compensation (De Zeeuw et al., 2003). Definitive resolution of this issue, like so many others in the field of gap junction neurobiology, awaits the development of rapid, effective, selective, nontoxic, reversible methods of blocking gap junction channels (Connors, 2012; Verselis and Srinivas, 2013).

Apropos of rhythmicity in the olivary nucleus, a recent study has nicely tested another longstanding idea about the role of electrical synapses. Although the olive has no inhibitory interneurons, it does receive a GABAergic input from axons originating in cerebellar nuclei (Sotelo et al., 1986). These inhibitory synapses terminate on the same distal dendritic spines that include the gap junctions coupling olivary neurons. The synaptic adjacency suggested to Llinás (1974) that activation of inhibitory inputs from the cerebellum might effectively shunt the current that otherwise allows electrical synapses to mediate olivary cell interactions, similar to a mechanism previously demonstrated in the *Navanax* nervous system (Spira and Bennett, 1972). Using modern tools of electrophysiology and optogenetics, Lefler et al. (2014) demonstrated that selectively activating the inhibitory inputs to the olive does indeed reduce

electrical coupling between its neurons, and also rapidly reduces or abolishes spontaneous subthreshold rhythms. Whether the loss of rhythms is due entirely to the uncoupling effect, or to contributions from other mechanisms such as general membrane shunting, is not clear. What is evident is that dendritic inhibitory synapses can quickly (in milliseconds), selectively, effectively, and reversibly influence electrical coupling between neurons without modulating gap junction channels directly. Judging from synaptic relationships in other parts of the brain, this could be a common mechanism.

Ironically, perhaps, too much electrical coupling may also be incompatible with neuronal rhythmicity under some circumstances. Ozden et al. (2004) used a hybrid model system consisting of an electronic (olivary neuron-like) oscillator coupled to an actual, living olivary neuron. They found that coupling strength could determine whether rhythms were synchronized, antisynchronized, or, at relatively strong coupling strengths, abruptly terminated—the so-called "amplitude death" regime.

Whether electrical synapses are essential for rhythm generation in vertebrate networks beyond the olivary nucleus is unknown. There is certainly enormous interest in the roles of electrical synapses in rhythms of the cerebral cortex, in particular, but the complexity of its circuits and their many oscillation types challenge experimentalists and theoreticians. Deletion of Cx36 abolishes nearly all electrical synaptic coupling between inhibitory interneurons of the cerebral cortex (Deans et al., 2001; Hormuzdi et al., 2001). It also reduces the power of gamma-frequency rhythms in the cortex *in vivo* (Buhl et al., 2003), an emergent network process that may require the synchronous activity of electrically coupled parvalbumin (PV)-expressing interneurons (Buzsaki and Wang, 2012). Although this suggests that electrical synapses between PV interneurons may be important for gamma rhythm generation, other experimental models of gamma-range activity have shown variable dependencies on Cx36 (Hormuzdi et al., 2001; Salkoff et al., 2015; Neske and Connors, 2016). The usual complicating factor applies; Cx36 knockout animals may express anomalous neural circuitry or intrinsic properties as they develop in the absence of most electrical synapses (Butovas et al., 2006; Postma et al., 2011).

Electrical synapses can enhance signal-to-noise ratios

Cellular processes are inherently noisy—membrane potentials vacillate as, for example, ion channels flip stochastically between open and closed states, signaling molecules trigger downstream cascades, and vesicles fuse and liberate transmitter (White et al., 2000; Sterling and Laughlin, 2015). As long as voltage noise occurs independently (asynchronously) in each cell of a network, coupling the cells with gap junctions will attenuate noise; currents are channeled into adjacent cells, and noise is essentially averaged across the network so that large fluctuations in any single cell are unlikely. The noise-reducing ability of electrically coupled networks of cells has been studied theoretically (e.g. Sherman et al. 1988; Usher et al., 1999; Medvedev, 2009). Behaviorally important signals can also be attenuated by gap junction coupling, but if signals are correlated across cells they will be reduced less than asynchronous noise. The consequence is that electrical synapses can improve signal-to-noise ratios in suitable circuits.

Neuronal gap junctions are pervasive in the retina, where they serve both to transmit specific sensory signals and to enhance signal strength relative to noise (Bloomfield and Völgyi, 2009; Massey, 2009). Retinal cones, photoreceptors that detect light of moderate to high intensity, are the best-studied example of signal-to-noise enhancement in electrically coupled neural networks. Cones are arranged in two-dimensional sheets interconnected by gap junctions (Baylor et al., 1971; Tsukamoto et al., 1992). You might expect that coupling among cones would diminish visual acuity. Overall, however, cone-to-cone electrical synapses optimize the spatial resolution of light detection by reducing noise, as demonstrated by orchestrated studies of cone morphology, electrophysiology, psychophysics, and computational modeling (Lamb and Simon, 1976; DeVries et al., 2002; Laughlin, 2002). Uncorrelated cone noise is sharply dissipated, because it tends to be cancelled out as it is shared by coupled cones. Light stimuli falling on the retina evoke cone receptor potentials that tend, unlike noise, to be correlated across local cone neighborhoods; correlated signals are dissipated much less than asynchronous noise. In essence, the cones tolerate a bit of visual blurring in order to gain a cleaner visual signal. By using electrical coupling the cone network can improve its signal-to-noise ratio by about 80% (DeVries et al., 2002).

Electrical synapses may also enhance signal-to-noise ratios in neurons other than photoreceptors, although direct evidence is limited. Again, the best studied circuits are in the retina (Bloomfield and Völgyi, 2009; Massey, 2009; Hartveit and Veruki, 2012; Völgyi et al., 2013). Rods—photoreceptors that operate at low light levels—can respond to single photons when dark-adapted. Rods are gap junction-coupled to one another and, as with cones, inter-rod coupling may improve signal-to-noise ratios under moderate light levels. Rods also synapse onto bipolar neurons, which in turn provide input to a type of inhibitory interneuron called the AII amacrine cell. AII cells synapse onto ganglion cells, the output neurons of the retina. AII amacrine cells are coupled to one another via Cx36-containing gap junctions, although when light levels are very low this gap junction coupling is minimized by a modulatory action of dopamine (Bloomfield et al., 1997); presumably that optimizes the sensitivity of the circuit to single photons. As background light rises moderately (“twilight” conditions), however, asynchronous noise generated by rods becomes significant and electrical coupling between AII amacrine cells increases. Inputs from multiple rods converge, via bipolar neurons, onto each amacrine cell. Modeling suggests that the coupling between AII amacrine cells can serve to suppress asynchronous noise more than light-triggered rod signals (Smith and Vardi, 1995). Indeed, when AII cells are uncoupled by knocking out Cx36 their noise levels double (Dunn et al., 2006), and the sensitivity of the most light-sensitive ganglion cells is reduced (Völgyi et al., 2004).

Experimental evidence for a signal-to-noise-enhancing function of electrical synapses outside the retina is scant. Examples include sets of coupled interneurons in the the antenna lobe of flies (Yaksi and Wilson, 2010), the olfactory bulb of fish (Zhu et al., 2013), and the locus coeruleus of primates (Usher et al., 1999). Considering the ubiquitous presence of biological noise in neural networks, it seems likely that noise reduction is a general function of electrical synapses throughout the brain. This is an issue ripe for a closer look.

Electrical synapses interact with intrinsic membrane excitability

The famously nonlinear electrical properties of most neuronal membranes lead to important and often complex interactions with synaptic inputs. Chemical synaptic inputs onto neuronal membranes have been studied extensively. Depolarization generated during an EPSP, for example, can activate postsynaptic voltage-gated channels that alter the size and time course of PSPs (Joyner and Westerfield, 1982; Westerfield and Joyner, 1982). Dendrites are particularly important sites for nonlinear interactions, since synapses densely innervate them and they often express a variety of voltage-gated ion channels. The activation ranges of these channels can overlap with voltages just above and below the resting membrane potential, so even small PSPs can influence channel gating. In dendrites of cortical pyramidal neurons, for example, EPSPs can activate voltage-gated sodium, calcium, HCN, or NMDA receptor currents that amplify and prolong postsynaptic events, and may even trigger local dendritic spikes (Spruston, 2008; Stuart and Spruston, 2015). EPSPs can also trigger opening of voltage- and time-dependent potassium currents that diminish and shorten postsynaptic events. Inhibitory chemical synapses, which generate hyperpolarization and conductance increases, can add further complexity and richness to dendritic interactions (Gidon and Segev, 2012).

Electrical synapses can also tap into these intrinsic membrane mechanisms. Studies of several types of neurons nicely illustrate the principle. Electrical PSPs of auditory axon terminals in goldfish are amplified by subthreshold sodium currents and diminished by potassium currents (Curti and Pereda, 2004). Inhibitory interneurons of the cerebellar cortex are often coupled by gap junctions (Mann-Metzer and Yarom, 1999). Action potentials in one interneuron evoke electrical PSPs in its neighbors, and these PSPs activate intrinsic membrane currents that amplify them. Consistent with this, when voltage-sensitive sodium channels of cerebellar Golgi cells (a type of inhibitory interneuron) are blocked with the local anesthetic QX-314, a sodium channel blocker, amplification of the PSPs is abolished (Dugué et al., 2009). Sensory neurons in the mesencephalic trigeminal nucleus are a particularly striking case (Curti et al., 2012). These cells are strongly connected by soma-to-soma gap junctions. Presynaptic action potentials trigger depolarizing electrical PSPs that activate persistent, voltage-dependent, QX-314-sensitive sodium channels in the postsynaptic membrane. The resulting inward sodium currents serve to amplify the PSPs and enhance synchronization. Inhibitory neurons of the thalamic reticular nucleus (TRN) tell a similar story. TRN cells are coupled by electrical synapses (Landisman et al., 2002), they also express a persistent sodium conductance, and when one TRN cell spikes tonically the electrical PSPs it generates activate postsynaptic sodium current (Haas and Landisman, 2012). That current can boost the electrical synaptic efficacy between TRN cells by as much as four-fold and enhance the synchrony of tonic spiking between TRN cells.

Dendrites with exceptionally strong voltage-dependent cation conductances allow electrical synapses to mediate particularly robust spike synchrony. The distal dendrites of mitral cells in the olfactory bulb, for example, can generate sodium and calcium-dependent action potentials (Bischofberger and Jonas, 1997; Chen et al., 1997). Branches of mitral cell dendrites that lie within single glomeruli are coupled by Cx36-dependent gap junctions and excitatory chemical synapses, while dendrites in different glomeruli are unconnected (Schoppa and Westbrook, 2001; Schoppa and Urban, 2003; Christie et al., 2005). Computational modeling suggests that

both active intrinsic conductances and the high input resistance of the dendrites contribute critically to the efficacy of dendro-dendritic electrical synapses in the bulb (Migliore et al., 2005). In addition, synchronization of somatic action potentials of mitral cells requires the concerted actions of electrical synapses and glutamatergic synapses colocalized in the dendrites (Schoppa and Westbrook, 2002; Christie et al., 2005).

The auditory brainstem circuit comprising fusiform and stellate neurons, mentioned above, provides a dramatic example of complex interactions between chemical synapses, electrical synapses, and intrinsic membrane mechanisms. Sensory axons can evoke fast glutamatergic EPSPs in the fusiform cells. This initial depolarizing EPSP—even when it is too small to reach action potential threshold—is boosted and prolonged by the activation of voltage-dependent sodium currents. The depolarization in turn causes deactivation of HCN cation channels, which lead to transient hyperpolarization (Apostolides and Trussell, 2014). The result is a slow, biphasic, noncanonical synaptic potential in the fusiform cell. This signal is then transmitted via electrical synapses to the stellate cells, where it generates excitation that is often strong enough to evoke spikes, followed by hyperpolarizing inhibition.

Electrical synapses at distal dendro-dendritic locations will be strongly influenced by their interactions with dendritic intrinsic membrane properties. However, many electrical synapses in vertebrate central circuits occupy positions adjacent to, or on, somata and axons. Examples include proximal dendro-dendritic gap junctions between some interneurons of the cat visual cortex (Fukuda, 2017), the soma-somatic junctions of mesencephalic trigeminal neurons (Curti et al., 2012), axo-dendritic junctions of fish and rodents (Korn and Faber, 2005; Pereda et al., 2004; Hamzei-Sichani, 2012; Nagy, 2012), and axo-axonic connections in rat hippocampus (Traub et al., 2002; Hamzei-Sichani, 2007). Proximity to axons offers electrical synapses rich opportunities for nonlinear interactions because axon initial segments, nodes of Ranvier, and presynaptic terminals may have exceedingly high densities of voltage-dependent sodium, potassium, and calcium channels, as well as high input resistances (Debanne et al., 2011; Bender and Trussell, 2012). For example, modeling studies and *in vitro* experiments suggest that axons with electrical synapses strong enough to mediate spike-to-spike transfer may generate fast oscillations in networks of the cerebral cortex (Traub et al., 2002; Simon et al., 2014).

Electrical synapses interact with chemical synapses

Electrical synapses are indifferent to the source of the electrical signals they transmit. One common source is chemical synapses, leading to the curious situation where chemically triggered PSPs are propagated through electrical synapses. Examples include depolarizing GABAergic PSPs passing from one hippocampal interneuron, through gap junctions, to another (Zsiros et al., 2006), and cholinergic PSPs passing between coupled spinal Renshaw cells (Lamotte d'Incamps et al., 2012). The general function of such an arrangement might be to equalize or distribute synaptic effects within a coupled network of neurons with similar functions, perhaps to enhance input sensitivity, or to reduce asynchronous synaptic noise.

Electrical synapses are often located closely adjacent to chemical synapses (Sotelo and Palay, 1970; Shapovalov and Shiriaev, 1980; Pereda et al., 2004; Hamzei-Sichani et al., 2007; Hamzei-

Sichani et al., 2012; Nagy, 2012; Rash et al., 2015; Rubio and Nagy, 2015). The two synapse types can often interact directly, in both directions, over a range of time scales, and in a variety of ways (O'Brien, 2014; Pereda, 2014; Haas et al., 2016; Pereda, 2016). Here I will focus on examples of electrical synapses that rapidly regulate chemical synapses.

The retina provides an instructive example of interaction between electrical synapses and the highly nonlinear mechanisms of neurotransmitter release from presynaptic terminals. Bipolar cells are electrically coupled to one another; this coupling allows networks of bipolar cells to integrate visual inputs from photoreceptors arrayed laterally across the retina. The bipolar cells also make excitatory glutamatergic synapses onto ganglion cell dendrites and, like most chemical synapses, these release their transmitter at rates that increase steeply as the presynaptic membrane depolarizes. The stage is thus set: laterally integrated electrical PSPs in bipolar cells can sharply modulate the release of glutamate onto ganglion cells by altering presynaptic membrane potential and thus the transmitter release mechanism (Demb and Singer, 2016; Kuo et al., 2016). The authors argue that this circuit arrangement increases the sensitivity of the retina to moving stimuli. Similar coordination between electrical and chemical synapses seems likely to occur in other types of central neural circuits.

A different style of interaction may mediate a form of lateral excitation in electrically coupled distal dendrites of mitral cells in the olfactory bulb (Christie et al., 2005). Activation of a glomerulus can trigger the synchronous spiking of mitral cells, and the actions of both electrical synapses and dendro-dendritic glutamate release are critical (Christie and Westbrook, 2006). The precise mechanism of interaction is not clear, but strong activity of mitral cells causes dendritic release of glutamate, which activates glutamatergic autoreceptors that depolarize the same dendrite. These depolarizations are communicated to neighboring mitral cell dendrites through electrical synapses.

Asymmetry and rectification in electrical synapses

The interactions between pairs of electrically coupled neurons are often unbalanced. There are two general underlying mechanisms: rectifying gap junction channels, and unequal cell sizes, shapes, or membrane properties. Rectification arises from heteromeric gap junction channels, i.e. channels with different subunit types expressed by the two participating neurons (Phelan et al., 2008; Marder, 2009). The resulting asymmetric channel structure leads to asymmetric gating mechanisms and voltage-dependencies (Palacios-Prado et al., 2014); the consequence is that current flows more easily in one direction than the other. The voltage-dependent gating kinetics of rectifying channels can be very fast (Jaslove and Brink, 1986).

Strongly rectifying electrical synapses have been observed more often in invertebrate than vertebrate nervous systems. The functions of rectifying junctions may include ensuring the unidirectionality of propagating signals, as in the motor circuits of the crayfish (Furshpan and Potter, 1959), and perhaps leech (Nicholls and Purves, 1970) and lamprey (Ringham, 1975). In this way, rectification makes an electrical synapse more similar to a chemical synapse, favoring one-way signal propagation. The analogy to chemical synapses fails when we consider hyperpolarizing signals such as IPSPs, however; a rectifying junction that favors depolarizing signals in one direction will also favor hyperpolarizing signal propagation in the other direction,

something very few chemical synapses can accomplish. Another function proposed for rectifying synapses is coincidence detection among convergent inputs to single neurons (Edwards et al., 1998; Marder, 1998).

Few examples of heterotypic, rectifying electrical synapses have been observed in vertebrate circuits. The most well characterized examples are the auditory nerve-to-Mauther neuron contacts in the goldfish brainstem (Rash et al., 2013). The polarity of rectification in these synapses is arranged such that they favor coincident auditory inputs, and thus may enhance the sensitivity of sensory transmission. This particular type of rectifying synapse is probably unique to teleost fish, because it is comprised of a heterotypic arrangement of two homologs (Cx35 and Cx34.7) of mammalian Cx36, which are not found in other vertebrates (Rash et al., 2013, 2015).

Another example of rectification has been observed between mammalian TRN neurons. Electrical synapses are common among TRN cells of wild-type mice, but only a small fraction of cell pairs are still electrically coupled in Cx36 knockouts (Landisman et al., 2002; Lee et al., 2014). Zolnik and Connors (2016) found that the electrical connections between TRN cells of the Cx36 knockout were significantly more asymmetric than wild-type connections. Asymmetry did not correlate with cell input resistances, and may derive from junctional rectification. The molecular basis of rectification in non-Cx36 TRN junctions is unknown.

Heterotypic gap junctions are not the only mechanism of electrical synapse asymmetry; one-sided post-translational channel modifications, such as junctional plasticity or modulation mechanisms (Pereda et al., 2004; Landisman and Connors, 2005), may also lead to asymmetry (Haas et al., 2011; Lefler et al., 2014; Palacios-Prado et al., 2014; Sevetson and Haas, 2015). These mechanisms have the potential for dynamically inducing and regulating asymmetry across nearly all types of electrical synapses.

Strongly asymmetric electrical coupling can also arise from differences in input resistances, which can derive from disparate cell sizes or membrane properties (Bennett, 1966, 1977). Heterologous electrical coupling—gap junctions between neurons of distinctly different types, and often sizes—is common in vertebrate central nervous systems. Examples include: many types of retinal neurons (Vaney, 2002; Veruki and Hartveit, 2002; Bloomfield and Volgyi, 2009), primary auditory axons and Mauthner cells in fish (Korn and Faber, 2005; Pereda, 2014), some mammalian auditory brainstem neurons (Apostolides and Trussell, 2013), spinal motor and sensory circuits (Kiehn and Tresch, 2002; Szczupak, 2016), and certain combinations of dissimilar inhibitory interneurons in the neocortex (Gibson et al., 1999; Galarreta and Hestrin, 2001; Simon et al., 2005) and hippocampus (Zsiros and Maccaferri, 2005).

An auditory circuit in the mouse cochlear nucleus illustrates some consequences of size asymmetry. Fusiform cells are much larger than the stellate cells they are coupled to, and stellate cells have much higher input resistances than fusiform cells (Apostolides and Trussell, 2013). This large resistive differential leads to strongly asymmetric electrical coupling that favors, by about four-fold, the transfer of voltage signals from fusiform cells to stellate cells over the reverse direction.

It is worth noting that electrical synapses with rectifying channels could, in principle, offset asymmetric coupling caused by different cellular input resistances to create more balanced bidirectional coupling.

CONCLUSIONS

The function of a synapse is to allow one cell to influence other cells. Electrical synapses—optimized for simplicity, efficiency, speed, and the artless conductance of nonspecific ionic current—might seem to have narrow functional potential. However, as electrical synapses are explored in an ever-widening range of circuits, we see that their roles go far beyond the early notions of speed and synchrony. Electrical synapses can excite, inhibit, synchronize and desynchronize, phase-shift, direct and redirect, detect coincidence, improve signal-to-noise ratios, grow and shrink, adapt, and productively interact with highly nonlinear membrane and synaptic mechanisms. Some of these functions have only been noticed in one or two specialized circuits so far, yet nearly all of them are likely to be more widespread.

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