Gap junction-mediated electrical transmission: Regulatory mechanisms and plasticity ☆

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A B S T R A C T

The term synapse applies to cellular specializations that articulate the processing of information within neural circuits by providing a mechanism for the transfer of information between two different neurons. There are two main modalities of synaptic transmission: chemical and electrical. While most efforts have been dedicated to the understanding of the properties and modifiability of chemical transmission, less is still known regarding the plastic properties of electrical synapses, whose structural correlate is the gap junction. A wealth of data indicates that, rather than passive intercellular channels, electrical synapses are more dynamic and modifiable than was generally perceived. This article will discuss the factors determining the strength of electrical transmission and review current evidence demonstrating its dynamic properties. Like their chemical counterparts, electrical synapses can also be plastic and modifiable. This article is part of a Special Issue entitled: The Communicating junctions, roles and dysfunctions.

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1. Introduction

In the nervous system, the term synapse applies to cellular specializations that provide a mechanism for communication between two neurons therefore facilitating the processing of information within neural circuits. This concept also applies to connections between a neuron and a muscle cell, gland cell or a cell of epithelial origin. It is accepted that there exist two main modalities of synaptic transmission: chemical and electrical. In chemical synapses, presynaptic electrical currents trigger the release of a transmitter molecule (neurotransmitter) that diffuses across the intercellular space to activate specific receptors located in the postsynaptic cell, which in turn generate a postsynaptic response. In the case of electrical synapses, gap junctions provide a direct pathway of low resistance for the spread of presynaptic electrical currents to the postsynaptic site. Most efforts have been dedicated to the understanding of the properties and modifiability of chemical transmission. In contrast, less is still known regarding the plastic properties of electrical synapses. Because of perhaps the relative simplicity of their underlying mechanism, it was generally perceived that electrical synapses lack plastic

properties. Rather than passive intercellular channels, electrical synapses proved to be dynamic and modifiable forms of interneuronal communication. The present report does not attempt to be a comprehensive review on the dynamic aspects of neuronal gap junctions, as we will not discuss regulation or their expression during development or as a result of brain injury. Rather, we will focus on some mechanisms that regulate coupling during some physiological processes. In this article we will first discuss the factors determining the strength of electrical transmission then review current evidence indicating that, as their chemical counterpart, electrical synaptic communication is highly dynamic and modifiable by various mechanisms.

1.1. Gap junctions as electrical synapses

In their classical 1959 paper David Potter and Ed Furshpan provided elegant evidence for the existence of electrical transmission between cells of the crayfish nervous system [1]. The search for the basis of electrical transmission greatly contributed to identifying the cellular structures that we know today as gap junctions. Gap junctions are clusters ("plaques") of hydrophilic intercellular channels formed by the docking of two ion channels or connexons, each contributed by a neighboring cell, allowing the direct transfer of signaling molecules and providing a pathway of low resistance for the spread of electrical currents between cells. The relationship of gap junctions with electrical transmission was established in seminal observations at identifiable synaptic contacts in teleost fish, where it was possible to correlate electrophysiological

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recordings with ultrastructural analysis. Together with specializations for chemical transmission, Robertson [2] found at auditory contacts on the goldfish Mauthner cell, known as Large Myelinated Club endings [3], areas of close membrane apposition that he described as "synaptic discs" (Fig. 1A) [the Mauthner cells are a pair of colossal reticulospinal neurons that mediate tail-flip responses in fish] [4,5]. Parallel investigations involving intracellular recordings by Furshpan [6] showed that, following stimulation of these terminals, the chemically mediated synaptic potential was preceded by a short-delayed brief depolarization, with properties which were not consistent with the criteria established for chemical transmission. Furthermore, Furshpan also showed that transmission at these contacts was bi-directional, as depolarizations originated postsynaptically could be detected with brief synaptic delays at presynaptic afferents [6]. Similar electrophysiological responses where simultaneously obtained by Bennett and colleagues from neurons of the electromotor system of electric fishes [7], where ultrastructural analysis revealed the presence of identical membrane appositions (Fig. 1B). We know now that those areas of close apposition, or "synaptic discs", correspond to gap junction plaques.

Connexons are hexameric ion channels formed by proteins that represent the products of two multigene families. While connexins (Cx) are unique to chordates, innexins and pannexins encode gap junction proteins in invertebrates, prechordates and chordates [8–10]. In mammals, only a small number of connexins were shown to be expressed in neurons: Cx36 [11], Cx45 [12], Cx50 [13,14], Cx57 [14] and possibly Cx30.2 [15] and Cx31.1 [16]. The number of neuronal connexins is higher in teleost fishes, which as a result of genome duplication have several homolog genes [17]. While some neuronal connexins are widely expressed others have a more restricted distribution [18]. Because of its widespread distribution and preferred neuronal expression [19], Cx36 could be considered the main "synaptic" connexin (see below). In contrast, Cx57 has been found restricted to horizontal cells in the retina [14]. Although pannexins 1 and 2 were found to be expressed in the vertebrate brain [20] and are likely to play important functional roles as hemichannels [21,22], there is no evidence at the present time indicating that these proteins form intercellular junctions between neurons. Innexins mediate electrical transmission in invertebrates and several members of this family have been identified in both Drosophila [23] and C. elegans [24]. Thus, the first electrical synapse reported by Furshpan and Potter [1] is mediated by innexin-containing junctions. Interestingly, and in contrast with connexins, some innexin genes are capable of giving rise to several partially identical transcripts that in turn translate into three distinct proteins [25], presumably increasing the functional diversity of electrical transmission.

1.2. Distribution and functional roles

Electrical synapses are ubiquitous in both invertebrates and cold-blooded vertebrates. Because of their reliability and lack of synaptic delay (relative to chemical synapses), electrical synapses are essential features in escape networks [5,26,27]. As a consequence of their bi-directionality, which allows sharing variations in the membrane potential between cells, they promote the coordinated activity of networks of extensively coupled neurons [28] and are also known to underlie mechanisms of lateral excitation in sensory systems [29–31]. Although most electrical synapses are bi-directional, rectification of electrical transmission has been observed in both in invertebrates [1] and vertebrates [32]. It is believed that rectification might result from differential properties of the pre- and postsynaptic elements at structurally asymmetric junctions [33].

As we mentioned earlier, initial evidence for the presence of electrical transmission was clearly established in invertebrates and cold-blooded vertebrates. In addition, following the classical description of electrical coupling in the chick ciliary ganglion [34,35], substantial evidence for the presence of electrical coupling and gap junctions was reported in the avian nervous system [36–38]. On the other hand, it was generally believed that electrical transmission was uncommon in mammals. The cloning of Cx36 led to great expansion of the known distribution of electrical transmission in the mammalian CNS [11]. Cx36 expression was identified by in situ hybridization in many mammalian CNS structures such as retina, hippocampus, cerebellum, neo-cortex, inferior olive and spinal cord, among others [39,40]. Cx36 specific antibodies and mice with markers replacing the Cx36 coding sequence are demonstrating the distributions more definitively. To date immuno-labeling combined with freeze fracture supports a purely neuronal distribution of Cx36 in the CNS [19,41] [but see 42]. Electrical coupling between cortical and thalamic interneurons and in inferior olive [43–46] is nearly absent in Cx36 knockout mice [45–48]. Electrical synapses have been shown to play important functional roles in retina [49], olfactory bulb [50], suprachiasmatic nucleus [51] and inferior olive [52], hippocampus [53] and cerebellum [54], amongst others, and Cx36-containing neuronal gap junctions have been reported in most of those regions [55–58]. Also, cortical gamma oscillations (30–80 Hz), which are thought to be essential for cognitive processing, are impaired in Cx36 knockout mice [47,48]. While in most cases electrical synapses act to promote coordinated neural activity [59], their presence was also shown to promote desynchronization in a cerebellar network [54]. Thus, rather specific or prevalent for a particular tissue or function, mammalian electrical synapses have proven to be almost as ubiquitous and functionally diverse as chemical synapses.

2. Factors that determine the strength of electrical transmission

2.1. Interplay between gap junctional conductance and membrane properties

Neurons operate by computing variations of the membrane potential evoked by synaptic currents and active processes. The change in the membrane potential observed by the spread of presynaptic currents through gap junctions to a postsynaptic neuron is usually referred to as a "coupling potential". The amplitude of this "coupling potential" does not solely depend on the conductance of the gap junction channels but also on the passive properties determined by the resistance and capacitance of the coupled neurons (Fig. 2A) [60]. In other words, the impact of gap junctional currents on a neuron's excitability, or its "synaptic strength", is dramatically influenced by non-junctional factors. Although changes in the membrane resistance
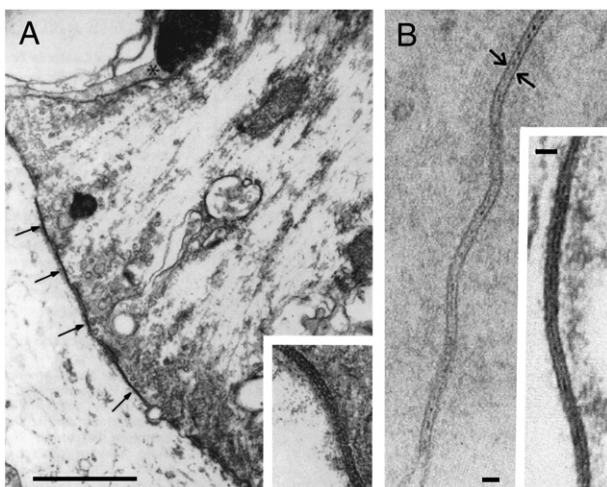

Fig. 1. Neuronal gap junctions constitute the basis for electrical synaptic transmission. A, Early electron micrograph of a club ending in goldfish revealing zones of close membrane apposition (arrows, inset), or "synaptic discs", later shown to be gap junction plaques. Calibration is 1 μm. B, High magnification of junctions between dendrites of spinal electromotor neurons in mormyrid fish. The plane of section is nearly perpendicular to the membranes and the overall thickness is about 140 A. Calibrations are 200 A. Panel A is modified from Robertson et al. [2]. Panel B is adapted from Bennett et al. [151].

A Determinants of the strength of electrical transmission

B Steady state Coupling Coefficient (CC):
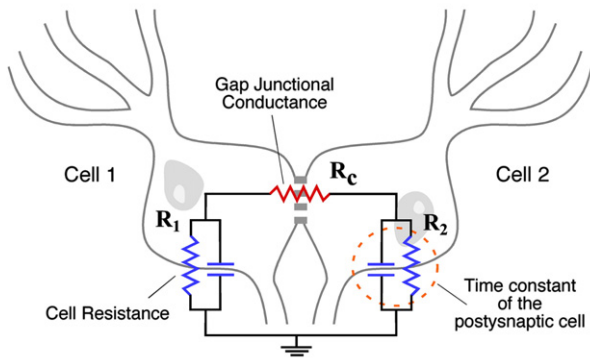
$$CC_1 = \frac{V_2}{V_1} = \frac{R_2}{R_2 + R_c} \qquad CC_2 = \frac{V_1}{V_2} = \frac{R_1}{R_1 + R_c}$$
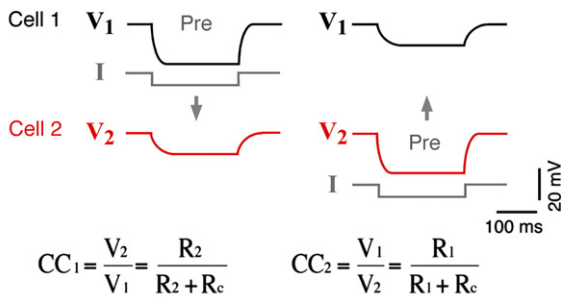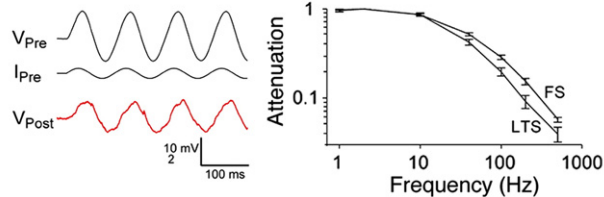
C Constraints imposed by passive properties

Fig. 2. Factors that determine the strength of electrical transmission. A, The cartoon represents a pair of coupled neurons on which an equivalent circuit of the key elements that determines strength of coupling was superimposed. The junctional conductance (Gap Junctional Conductance) is represented by a lumped resistance (Rc), whereas the passive properties of coupled cells are represented by a resistor (R1, R2) in parallel with a capacitor, which together determine the input resistance and the time constant of the neuron. B, The steady state coupling coefficient. The strength of electrical synapses can be assessed by the injection of long polarizing current pulses in one of a pair of coupled neurons. Current injection evokes a voltage drop in the presynaptic cell (Pre), which is typically accompanied by a change of the membrane potential in the coupled cell of lower amplitude, slower temporal course and similar polarity. The duration of the current pulses is usually long enough to overcome the initial attenuation of the membrane potential produced by the filtering properties imposed by the passive properties of the postsynaptic membrane, so voltage changes can be measured at "steady state". The strength of coupling is quantified by calculating the coupling coefficient (CC), defined as the ratio between the voltage deflections in the post- and presynaptic cells. As it can be observed, at steady state conditions this coefficient critically depends on the resistance of the postsynaptic cell. C, Constraints imposed by the time constant of the postsynaptic cell. Due to low-pass filtering properties of the coupled neurons, time varying signals are attenuated according to their frequency content. Left, Injection of sine wave current in the presynaptic cell (I_Pre) evokes a sinusoidal variation of the membrane potential of the presynaptic cell (V_Pre) that can be recorded as a coupling potential in the postsynaptic cell (V_Post). Right, Frequency transfer characteristics determined for pairs of electrically coupled fast-spiking (FS) and low-threshold spiking (LTS) inhibitory interneurons of neocortical layer 4 in the rat. Magnitude of transfer represents the ratio of membrane potential amplitude in the postsynaptic cell over that of the presynaptic cell, during sine wave injections of various frequencies at the presynaptic side, indicates that electrical contacts between pairs of FS and LTS interneurons behaves as low-pass filters. These results indicate that the strength of electrical coupling is stronger for presynaptic signals of lower frequency content. Modified from Gibson et al. [152].

and capacitance of the postsynaptic neuron would also affect chemical synaptic transmission, their influence seems to be critical in the case of electrical synapses, which unlike chemical synapses, lack postsynaptic mechanisms of amplification of presynaptic signals. Finally, the terms "electrical coupling" and "electrical synapses" are not interchangeable because neuronal gap junctions could also provide a conduit for the passage of small regulatory molecules to activate intracellular signaling cascades at the postsynaptic cell, as proposed to occur during development [61].

With the purpose of their characterization, electrical synapses are generally explored by injecting a depolarizing or hyperpolarizing current into one of the coupled cells while recording variations in the membrane potential of both the presynaptic and postsynaptic cells (Fig. 2B). [Given that most electrical synapses are bi-directional the use of pre- and postsynaptic terminology is arbitrary and only applies to the cell in which signals were generated. Furthermore, and more importantly, when a "presynaptic" action potential propagates to the "postsynaptic" cell, the membrane resting potential of the "postsynaptic" cell simultaneously propagates to the "presynaptic" cell.] The duration of the current pulses is usually long enough to overcome the initial attenuation of the membrane potential produced by the filtering properties imposed by the passive properties of the postsynaptic membrane, so voltage changes can be measured at steady state (Fig. 2B). The steady-state "coupling coefficient" is a measure of the strength of the electrical synapse and is defined as the ratio between the voltage deflections in the post- and presynaptic cells, both measured at steady-state, that is, once membrane capacitance is charged and therefore current flows only through the resistor (Fig. 2A). As can be inferred from Fig. 2B, the steady-state coupling coefficient is influenced not only by the resistance of the gap junction (Rc) but also by the resistance of the postsynaptic cell (R). Thus, two gap junctions with identical conductance will have dramatically different coupling coefficients if the resistances of the postsynaptic cells are substantially different. The cell resistance is determined by a combination of factors including membrane resistivity and cellular geometry. This resistance can be different from the experimentally estimated input resistance, which is also affected by the gap junctional resistance and the resistance of the coupled cell. Indirect measurements of junctional conductance can be derived from estimates of steady-state coupling coefficients and the cell's resistance [60]. These estimates of junctional conductance assume that the values of the input resistance of the coupled cells measured experimentally at the cell's soma represent the resistance influencing electrical coupling. This is not a trivial consideration in most mammalian and invertebrate neurons where gap junctions may be located at remote dendro-dendritic compartments.

Because most naturally occurring neuronal signals are brief, the strength of electrical transmission is generally affected by the time constant of the postsynaptic cell (Fig. 2B) usually of relatively longer duration, which determines the speed at which voltage changes in response to a particular current. The properties of an electrical synapse in the frequency domain can be explored by applying sinusoidal currents of various frequencies in the presynaptic cell while comparing changes in the membrane potential at both the pre- and postsynaptic cells. The coupling coefficient for low frequency sinusoids equals or approximates to that measured at steady state, whereas that obtained using sinusoids of higher frequencies diminishes progressively (Fig. 2C). Thus, in most mammalian neurons, which have membrane time constants (estimated with the whole cell technique) in the order of tens of milliseconds, electrical synapses behave as low-pass filters [28]. It is important to emphasize that this property does not rely on the properties of the gap junction itself but on the passive properties of the coupled cell [60]. Interestingly, likely as a result of the increased background synaptic activity, estimates of time constant obtained in vivo were shown to be much faster than those obtained in vitro [62], suggesting that transmission of fast signals might be stronger under in vivo conditions. Finally, low-pass filtering

properties of electrical synapses are virtually inexistent in cells with unusually brief time constants such as the Mauthner cell (see below).

2.2. Are electrical synapses excitatory or inhibitory?

With the exception of the unusual strongly rectifying synapses [1], the sign of the electrical synaptic potentials critically depends on the characteristics of the presynaptic signal that occurs under physiological conditions. The coupling produced by naturally-occurring changes in the membrane potential of the presynaptic cell, such as action potentials [28,45,59] and synaptic potentials [63], represents the physiologically relevant signals and therefore deserves the name of "electrical postsynaptic potential" (see below). Because of the slow time constant of most neurons, presynaptic signals with higher frequency content (such as action potentials) are greatly attenuated and thus the coupling coefficient estimated from an electrical synaptic potential, generally referred to it as "spikelet", is usually of smaller value than that estimated from steady-state coupling coefficients. In contrast, although of substantially smaller amplitude at the presynaptic cell, longer-lasting signals with lower frequency content such as the afterhyperpolarization (AHP) which follows some action potentials or synaptic potentials, are less attenuated and therefore, paradoxically, more likely to influence the postsynaptic cell [28,59,64]. This property is critical when presynaptic neurons fire trains or "bursts" of action potentials. Spikelets evoked by a burst of presynaptic action potentials associated with less pronounced AHPs can temporally summate to evoke a sizable depolarization in the postsynaptic cell [45,65]. In contrast, presynaptic action potentials with pronounced and long-lasting AHPs will produce a hyperpolarization of the postsynaptic cell [28,64]. Because the action potential is significantly more filtered than the much longer lasting AHP, this last hyperpolarizing presynaptic signal predominates and the result is a brief depolarization followed by a much larger and longer hyperpolarization, which can be long during sustained presynaptic repetitive discharges [64]. This hyperpolarization has been shown to play an important functional role promoting desynchronization in cerebellar networks [54]. Thus, depending on the characteristics of the AHP currents in the presynaptic cell, electrical synapses can either excite or inhibit the postsynaptic cell. The definition of excitatory or inhibitory action based on the predominance of depolarization or hyperpolarization is in any case arbitrary, as inhibitory hyperpolarizing conductances were also shown to trigger rebound spikes in some cell types [66]. Finally, beyond the fact that electrical coupling can in adequate contexts produce excitatory or inhibitory effects (effects that are relative to the spike threshold of the neuron), electrical synapses were postulated to be "synchronizing" [59], a denomination that emphasizes the virtues of their bi-directional properties.

3. Regulation of electrical coupling by the non-junctional membrane

We discussed in previous sections how the strength of an electrical synapse could be influenced by gap junctional and non-junctional factors. We will review now some examples indicating that, indeed, the strength of electrical transmission can be modified by regulation of both gap junctions and the non-junctional membrane.

3.1. Regulation of electrical coupling by the non-junctional membrane

3.1.1. Regulation of electrical coupling by neighboring inhibitory chemical synapses

Because the electrical coupling critically depends on the resistance of the postsynaptic cell, changes in this resistance will result in increases or decreases of the amplitude of the coupling potential. Chemical inhibitory transmission often works by producing a "shunting" effect, that is, the inhibitory synaptic conductance short-circuits the currents that are generated at adjacent excitatory synapses. While shunting would reduce both chemically and electrically mediated synaptic potentials,

there exist a few examples in which the anatomical arrangement clearly suggests that its action is intended to regulate the strength of electrical coupling between two neurons. The most notorious example is the inferior olive, a structure where electrical transmission constitutes the only form of synaptic communication between its principal cells [67], and where clusters of synchronized neurons are dynamically sculpted as a result of transient regulation of electrical coupling [68,69]. This regulation takes place at the glomerulus, an anatomical structure where coupled dendritic processes of inferior olivary neurons and afferent chemical synaptic contacts co-exist [67]. Here, release of GABA from terminals of axons originating in the deep cerebellar nuclei has been proposed to indirectly regulate coupling by shunting depolarizing currents in dendritic processes of inferior olivary neurons [67,68] (Fig. 3A). The time window of this "uncoupling" is determined by the duration of the shunting synaptic conductances, which while unusually long due to de-synchronized transmitter release [70], lasts only tens of milliseconds. By promoting synchronous complex spikes that influence sets of Purkinje cells in the cerebellar cortex, these quickly and transiently-formed compartments (whose size is sensitive to picrotoxin and gap junction blockers) (Fig. 3B–D) are thought to encode important functional parameters that influence the cerebellar cortex [69], suggesting that the formation of groups of functionally interconnected neurons underlies essential aspects of the inferior olive function. Similarly, inhibitory synapses were shown to regulate the strength of electrical coupling between the expansion motoneurons of the mollusk *Navanax* [71].

3.1.2. Interaction with intrinsic membrane properties

Most neurons are endowed with specific complements of intrinsic membrane properties, which determine their individual electrical phenotypes. Most of these properties represent voltage-dependent conductances that impart non-linear behaviors to membrane responses. Thus, electrical coupling could be enhanced or reduced by the closing or opening of potassium (K^+) conductances in a voltage-dependent manner, which affect the input resistance of the coupled cells. In other cases, voltage-dependent conductances act to amplify electrical coupling, by adding an additional depolarization to that produced by the coupling itself. This is the case of the subthreshold sodium (Na^+) currents, which were shown to amplify electrical coupling in several cell types [31,72–75]. One example is the voltage-dependence of coupling observed at the previously mentioned goldfish mixed synapses known as Club endings [31], which provided one of the first examples of electrical transmission in vertebrates (Fig. 1A). At these afferents, the amplitude of the coupling potential produced by the retrograde spread of signals from the postsynaptic Mauthner cell (Fig. 4A) is dramatically enhanced by depolarization of the presynaptic terminal (Fig. 4B). The membrane time constants of these afferents and the coupled Mauthner cells are very fast (estimated of ~400 μs in the Mauthner cell) and therefore the coupling of action potentials does not result attenuated as in most mammalian neurons [31]. This voltage-dependent enhancement of electrical coupling does not represent a property of the junctions themselves but the activation of a subthreshold Na^+ current present at presynaptic terminals that acts to amplify the synaptic response and can be blocked by both extracellular TTX and intracellular application of QX-314 [31]. Interestingly, the interplay of this current with low threshold repolarizing K^+ conductances reproduces closely the waveform of the coupling recorded at resting potential (Fig. 4C) [31]. Retrograde electrical communication at these afferents is thought to play an important functional role as a mechanism of lateral excitation, promoting cooperativity between afferents. Like in the Mauthner cell, amplification of electrical coupling by intrinsic membrane properties can improve communication between neuronal processes of dissimilar size and shape, which are unfavorable for bi-directional communication. Similar amplification of electrical coupling by subthreshold Na^+ current has been reported in the mammalian cerebellum [72,73] and in the mesencephalic nucleus of the Trigeminus
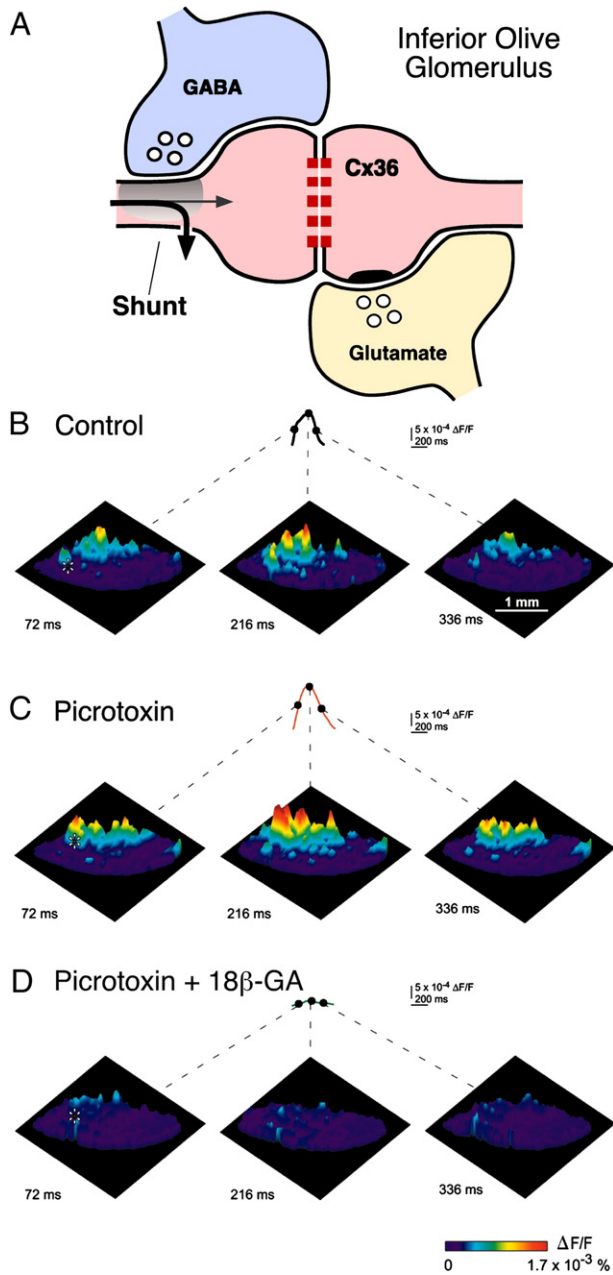
Fig. 3. Regulation of the electrical coupling y changes of the non-junctional membrane. A, The inferior olive glomerulus: inhibitory (GABA, blue) and excitatory (glutamate, yellow) synapses terminate in the vicinity of gap-junctions between dendrodendritic processes (spine) of inferior olivary neurons (pink). Inhibitory synaptic conductances are thought to briefly shunt excitatory currents, temporarily reducing effective electrotonic coupling between IO neurons. B–D, Optical recordings with high speed voltage-sensitive dye imaging, in vitro, describe patterns of ensemble oscillatory activity in the inferior olive. B, Optical recordings were cut into fragments of two or three oscillatory cycles and averaged based on the temporal profile of intracellular recordings (see Ref. [69] for details). C, Application of the GABA$_A$ receptor blocker picrotoxin enhances oscillatory clusters. D, These clusters are absent in slices treated with the gap-junction blocker 18β-glycyrrhetinic acid (18β-GA). The three representative images show the location and spatial spread of 1 oscillatory cycle. The amplitude and time-course of the optical responses for 1 pixel are also shown (asterisk in each left image). The time points for each image are labeled on the pixel trace; the start of the oscillatory cycle was defined as 0 ms.
Modified from Leznik and Llinas [69].

(MesV) [74], and thalamic relay nucleus [75] where electrical coupling of presynaptic spikes was shown to be amplified in a voltage-dependent manner by postsynaptic cells (Fig. 4D, left). Such amplification was no longer observed when QX-314 was added to the recording electrode

solution (Fig. 4D, right). Interestingly, due to the pronounced after-hyperpolarization of the presynaptic action potential in cerebellar Golgi cells, electrical coupling was predominantly hyperpolarizing at hyperpolarized membrane potentials, whereas it became depolarizing as a result of the action of the subthreshold Na$^+$ current, at more depolarized potentials [72]. Electrical coupling in these cells could be excitatory or inhibitory, depending on the resting potential of the cell, and this sign reversal was blocked by QX-314 (Fig. 4E). Furthermore, electrical coupling between MesV neurons is enhanced in a frequency-dependent fashion by cellular properties that endow these cells with electrical resonance and which include a persistent Na$^+$ current and a subthreshold K$^+$ current [74]. Remarkably, the amplitude of the transfer was higher at frequencies near 50 Hz than that obtained at steady-state conditions (Fig. 5B), indicating that transmission of electrical signals between MesV neurons exhibits some degree of frequency preference, and therefore do not behave as simple "low-pass" filter. Thus, the efficacy of an electrical synapse can be dynamically shaped in a voltage-dependent manner by properties of the non-junctional membrane.

3.2. Gap junctional conductance is dynamically regulated

We have considered so far how non-junctional factors affect the degree of electrical coupling between neurons, as a mechanism to regulate the strength of electrical transmission. In addition to these factors, electrical synapses have been proven to be extremely dynamic as a result of modification of the gap junction channels themselves.

3.2.1. Modulation by neurotransmitter modulators

The retina provided the first examples for the existence of regulation of gap junctional conductance. That is, dopamine was shown to promote reduction of tracer and electrical coupling (Fig. 6A) between horizontal cells [76–81]. Dopamine was shown to mediate this action via activation of D1 receptors, which led to an elevation of cAMP which in turn activates cAMP-dependent protein kinase A (PKA) [76–82]. The effects of dopamine in retina are not to be restricted to this cell type, and this neurotransmitter modulator was also shown to regulate electrical coupling in AII amacrine cells [83–85]. In contrast to horizontal cells, at which electrical coupling is mediated by Cx57 (Cx55.5 in teleost), coupling between Amacrine type II cells is primarily mediated by Cx36. Two PKA phosphorylation sites were identified in Cx36 and its fish homologs: Ser110 and Ser293 (Ser276 in teleost) [86,87], which are essential for PKA-mediated regulation of coupling. These two sites were shown to undergo dynamic changes in the phosphorylation state in retina [49,88] and to underlie important functional roles in both AII amacrine cells [88] and photoreceptors [89]. The retina also provided some of the clearest examples of the functional role of the regulation of electrical synapses. Because dopamine release is modulated by light, coupling between AII amacrine cells, as well between horizontal cells, changes with different degrees of luminance. Remarkably, AII amacrine cells show small receptive fields under darkness or daylight but larger receptive fields and enhanced coupling at intermediate levels, such as dim background light or twilight. In other words, light acts to reconfigure networks of electrically coupled neurons through the action of dopamine. [49] [For a complete review on regulation of electrical coupling in retina see ref. [49]] The regulatory role of dopamine at electrical synapses was shown to be widespread and observed at both vertebrate [76–85,90–92] and invertebrate [93,94] nervous systems. Further, the regulatory effects of PKA on electrical conductance were also observed to occur following the activation of noradrenergic receptors (Fig. 6B), which dynamically regulate the degree of coupling between inhibitory interneurons in hippocampus [95]. Other neurotransmitters such histamine [49,96] acting via different second messenger pathways such cGMP [83,96,97] and nitric oxide [97,98] were reported to regulate the degree of coupling by targeting junctional conductance. In summary, neurotransmitter modulators can regulate the
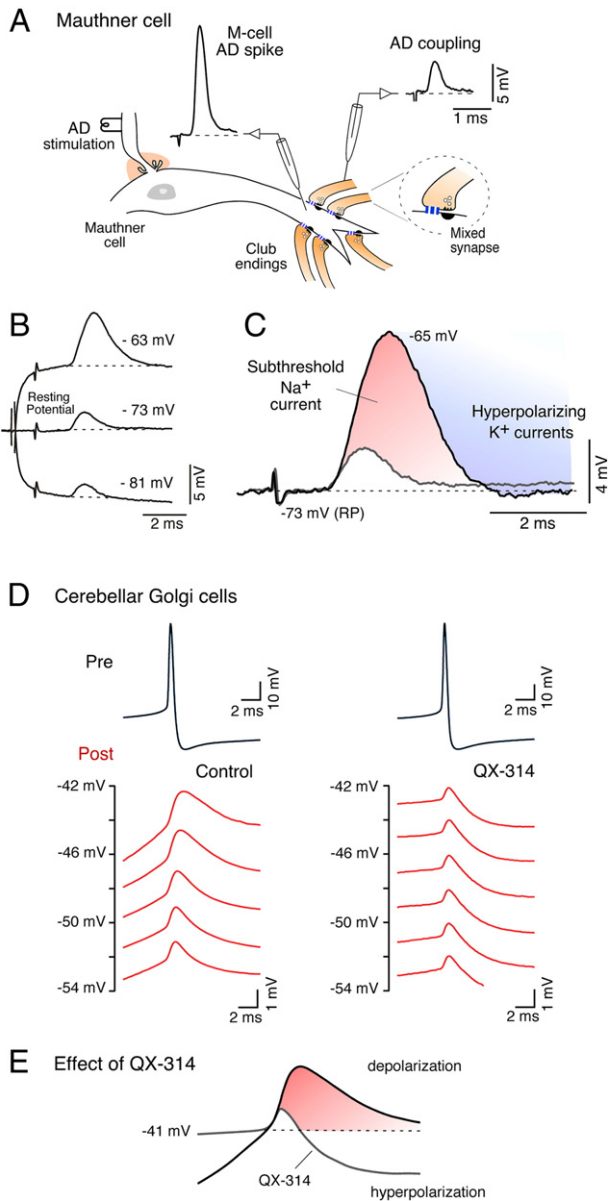
Fig. 4. Enhancement of electrical coupling by intrinsic membrane properties. A, Auditory afferents (club endings) terminate as mixed synapses (mixed synapse) on the lateral dendrite of the goldfish Mauthner cell. The action potential produced by the antidromic stimulation of the Mauthner cell axon in the spinal cord (M-cell AD spike) can be recorded as a coupling potential in the presynaptic afferents (AD coupling). B, The amplitude of the AD coupling is voltage-dependent; it increases with presynaptic membrane depolarization and decreases with membrane hyperpolarization (current pulses of ± 0.9 nA). C, Superimposed traces illustrate the AD potential obtained at resting potential (RP, −72 mV) and at a depolarized potential (−65 mV). Enhancement of AD coupling results from the interplay between a subthreshold Na^+ current (red), that adds to the depolarization produced by the coupling, and a delayed repolarizing K^+ conductance (blue), which by terminating the action of the subthreshold Na^+ current, reproduces the waveform of the AD coupling obtained at resting potential. D, Voltage-dependent amplification of coupling between pairs of electrically coupled Golgi cells in the rat cerebellar cortex. Depolarizing coupling potentials recorded in the postsynaptic cell (Post) in response to action potentials generated in the presynaptic cell (Pre). Recordings were obtained in control conditions (left), and when the Na^+ channel blocker QX-314 was included in the recording electrode of the postsynaptic cell (right). In control conditions, depolarizing coupling potentials were progressively bigger with postsynaptic cell depolarization. Such amplification was absent when QX-314 was added to the postsynaptic recording electrode, suggesting the participation of a subthreshold Na^+ current whose activation at subthreshold membrane potentials enhances coupling potential amplitude. Because of the pronounced afterhyperpolarization of the presynaptic action potential, electrical coupling was predominantly hyperpolarizing at hyperpolarized membrane potentials, whereas it became depolarizing as a result of the action of the subthreshold Na^+ current, at more depolarized potentials. This sign reversal was blocked by QX-314, indicating the critical functional role of the subthreshold Na^+ current (E). Panels A–C is modified from Curti and Pereda [31]. Panels D and E modified from Dugue et al. [72].
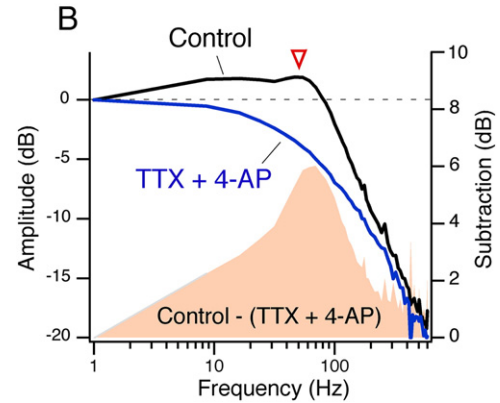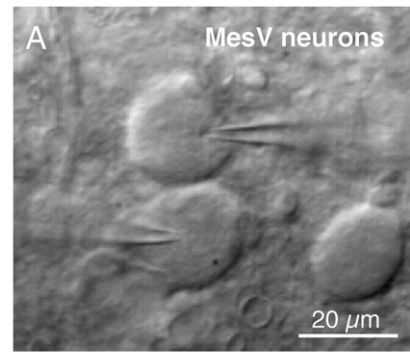

Fig. 5. A, Intrinsic membrane properties enhance the transfer of relatively high-frequency signals. A, IR-DIC image of a pair of contiguous MesV neurons during a simultaneous whole-cell recording. B, Frequency transfer properties in a pair of electrically coupled MesV neurons using a sinusoidal current of increasing frequency (zap). Magnitude of the transfer under control conditions and after the extracellular application of TTX and 4-AP. The amplitude of the frequency-transfer characteristics was calculated as the ratio of the Fast Fourier Transform (FFT) of the postsynaptic cell over the FFT of the presynaptic cell. The solid pink area represents the difference in transfer in the two conditions, illustrating the contribution of active mechanisms to frequency-transfer characteristics, particularly at ~50 Hz (arrowhead).
Modified from Curti el al. [74].

degree of coupling between neurons by targeting gap junctional conductance. These regulatory molecules lead in most cases to state-dependent reversible effects on the strength of electrical synapses.

3.2.2. Activity-dependent regulation of gap junctional conductance

The strength of electrical synapses was also shown to be modified by the activity of glutamatergic synapses [99–104]. Experiments at club endings (mixed synapses on the goldfish Mauthner cell; Figs. 4A and 7A) demonstrated that gap junctional conductance at these contacts (as well as efficacy of chemical transmission) can be modified by afferent activity in the form of both short- [100] and long-term potentiation [99,100] and long-term depression [101,104]. Club endings are advantageous for correlations of their structural and biochemical features with their in vivo physiological properties and provide a valuable model for the study of vertebrate electrical transmission [105]. These terminals are unusually large (5–10 μm in diameter), and each has ~100 GJ plaques and up to ~100,000 channels [106], containing Cx35 [107], a fish homolog of the mammalian neuronal connexin Cx36 [108]. Recent data indicate that a second homolog of Cx36, Cx34.7, is also present at these terminals [109]. The induction of activity-dependent long-term potentiation (Fig. 7B) requires high frequency stimulation of these synapses (brief trains of 2 to 8 stimuli at 500 Hz; "500 Hz burst" protocol) and was blocked by postsynaptic injections of BAPTA and by superfusion of the medulla with NMDA receptor antagonists [99,100]. Activation of NMDA receptors leads to a localized increase in the intracellular concentration of Ca^{++}, which in turn
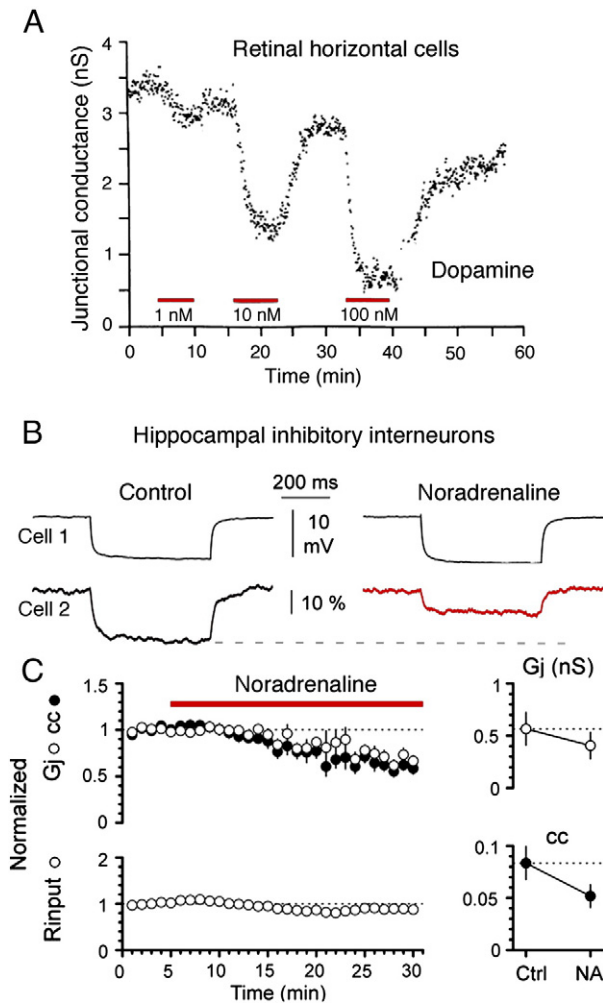
Fig. 6. Neuromodulators regulate electrical transmission. A, Dopamine reduces junctional conductance between pairs of catfish horizontal cells in a dose-dependent fashion. Dopamine (1, 10 and 100 nM) was added to the extracellular solution during the intervals indicated by the red bars. Junctional conductance (nS) is plotted as a function of time. B, Electrical coupling between stratum lacunosum-moleculare interneurons is modulated by α-adrenergic receptors. Application of noradrenaline (20 μM) reduces the junctional conductance and the coupling coefficient. C, Time course of the effects of noradrenaline on the normalized junctional conductance and the coupling coefficient and input resistance. Panel A is modified from DeVries and Schwartz [80]. Panels C is modified from Zsiros and Maccaferri [95].

activates the kinase Ca^{++}-calmodulin-dependent kinase II (CaMKII) [110], whose activity is necessary for the potentiation (Fig. 7C). Simultaneous pre- and postsynaptic recordings at these single terminals demonstrated that such functional interaction takes place in the same ending, within a few micrometers [101]. Accordingly, confocal and freeze fracture immunolabeling (FRIL) of these terminals showed that the NR1 subunit of the NMDA glutamate receptor, proposed to be a key regulatory element, is present at PSDs closely associated with gap junction plaques containing Cx35 [105,107]. Thus, activity-dependent modulation of electrical coupling results form an interaction with nearby glutamatergic synapses, which in addition to modifying their own strength, also target nearby gap junctions. It was recently reported that, in similarity with the club endings, presynaptic activity of glutamatergic ON bipolar cells increased phosphorylation of Cx36 in AII amacrine cells and this phosphorylation was dependent on activation of NMDA receptors and mediated by CaMKII [111]. In contrast with the Mauthner cell, NMDA receptors were in this case located extra-synaptically and co-localized with Cx36 on AII amacrine cells [111].

CaMKII has been implicated in mechanisms of activity-dependent plasticity in chemical synapses [112–115]. This kinase is an essential and abundant component of glutamatergic postsynaptic densities (PSDs) [116] in which it associates with other proteins, such as NMDA receptors [116,117,118]. Interestingly, recent data indicate that this kinase can also molecularly interact with Cx36 [119] and electrical transmission at club endings is mediated by fish homologs of the Cx36. That is, CaMKII was shown to bind to two cytoplasmic domains of Cx36. Both domains reveal striking similarities with segments of the regulatory subunit of CaM-KII such as the pseudosubstrate and pseudotarget sites of the kinase [119]. Furthermore, similar to the NR2B subunit of the NMDA receptor, both Cx36 binding sites exhibit phosphorylation-dependent interaction and autonomous activation of CaMKII [119]. This report also revealed the existence of multiple phosphorylation sites for αCaMKII in Cx36 [119]. In silico analysis showed that Cx36 shares most of the identified residues with its fish homologs Cx35 and Cx34.7 [120]. This analysis also showed that residues S315/S298/S300 in Cx36, Cx35 and Cx34.7, respectively, constitute exclusive phosphorylation sites for CaM-KII that are not shared with other kinases. On the other hand, residues S110 and S293 in Cx36, S110 and S276 in Cx35, and S110 and S277 in Cx34.7, are shared with PKA [82,86,108,121].

A second form of activity-dependent potentiation, which follows a different induction protocol and signaling mechanisms, was more recently reported at club endings [122]. In this case brief continuous stimulation of these afferents at 100 Hz (100 Hz protocol) (Fig. 7D), which leads to release of endocannabinoids via activation of mGluR receptors and dendritic depolarization, triggered a long-term enhancement of both components of the synaptic response [122]. This phenomenon requires the activation of CB$_1$ receptors and is indirectly mediated via the release of dopamine from nearby varicosities, which in turn led to potentiation of the synaptic response via a PKA postsynaptic mechanism [122] (Fig. 7E). Thus, dopamine availability can be regulated by the activity of nearby glutamatergic synapses. Two aspects of the action of dopamine on these terminals are unusual: 1) in contrast to most examples dopamine produces enhancement of gap junctional conductance, and 2) rather than a modulator dopamine (presence required) acts as a trigger, initiating a long-term modification of electrical transmission [91,92,122]. That is, a local brief application of dopamine in the vicinity of these terminals (puff) was sufficient to trigger a lasting potentiation of both components of the synaptic response [91,92].

Interestingly, the activity of the glutamatergic synapses localized within the same contact at club endings (Fig. 8A), creates a wide diversity of coupling between each of these terminals and the lateral dendrite of the Mauthner cell (Fig. 8B, C) [101]. Because induction of modulation of electrical coupling at goldfish mixed synapses (500 Hz burst protocol) occurs postsynaptically [110], short-range functional interactions may not be limited only to mixed synapses but may be found where glutamatergic synapses are close to gap junctions formed by other presynaptic elements. Consistent with this possibility, FRIL analysis revealed the proximity of NR1-containing PSDs to Cx36-containing gap junctions in the inferior olive [123], at distances comparable to separations between the chemical transmitting domains and gap junctions in goldfish mixed synapses (Fig. 8D), suggesting that similar interactions between electrical and glutamatergic synapses might occur in the inferior olive. Accordingly, as with the Mauthner cell with club endings, single olivary neurons were found differentially coupled with each of its partners (Fig. 8E) presumably as a result of local, glomerulus-specific, regulation of coupling [123]. Several lines of evidence support this possibility: 1) Cx36 and Cx35 are highly homologous and share regulatory sequences for CaMKII [120]; 2) CaMKII was shown to co-localize with both Cx36 in the inferior olive [119] and Cx35 in goldfish mixed synapses [120]; 3) CaMKII associates with both Cx36 [119] and Cx35 [120], and 4) the association of CaMKII with Cx35 is believed to be indicative of the degree of potentiation of electrical transmission at goldfish mixed synapses [120]. Also supporting this possibility, a recent report suggests
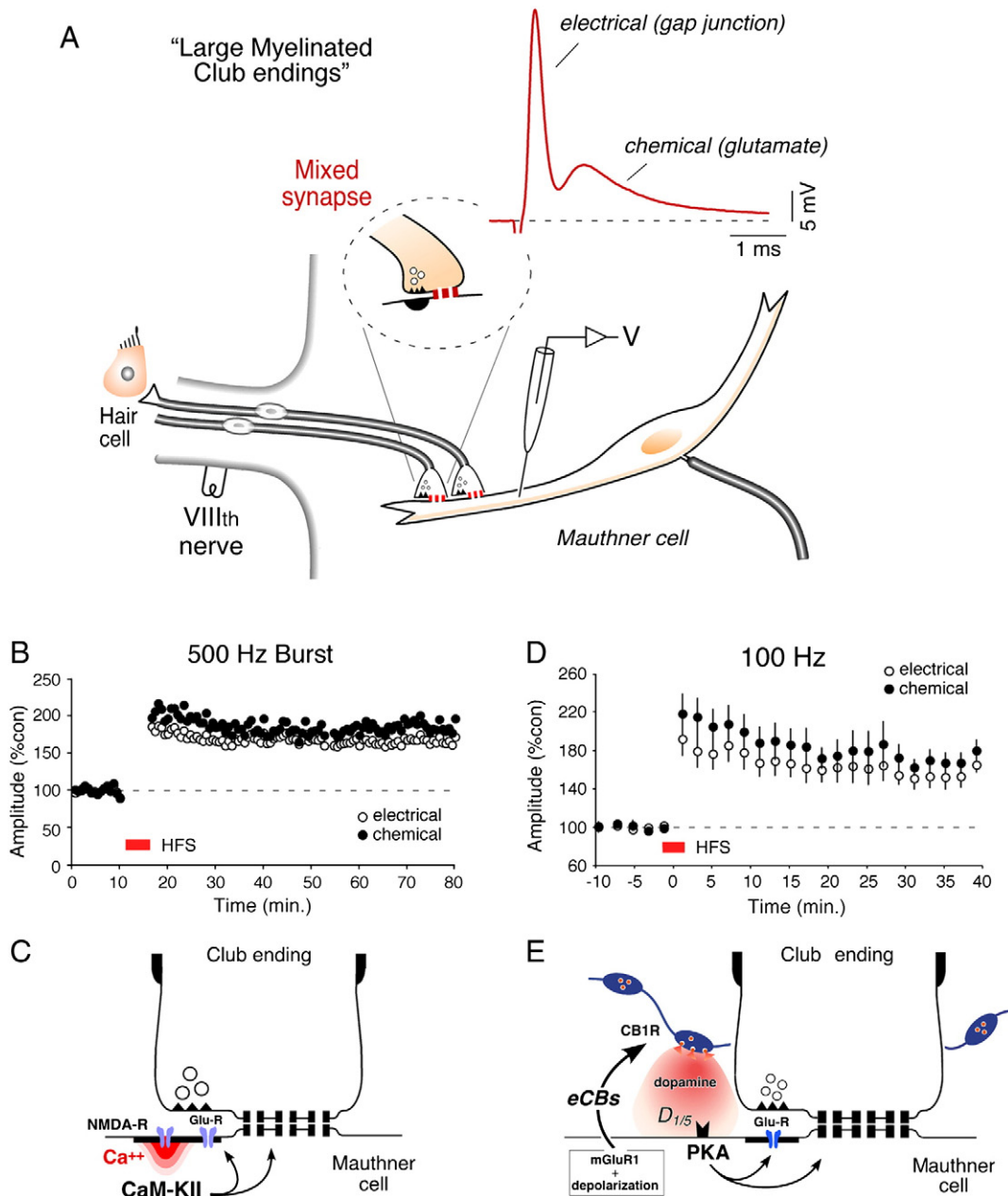
Fig. 7. Activity-dependent plasticity of electrical transmission a primary auditory afferents on the goldfish Mauthner cell. A, Club endings exhibit mixed synaptic transmission. Typical experimental arrangement showing VIIIth nerve auditory primary afferents (which contact saccular hair cells; "hair cell") terminating as club endings on the ipsilateral Mauthner cell lateral dendrite. VIIIth nerve and postsynaptic electrodes are indicated. Inset: cartoon represents a club ending, at which both mechanisms of synaptic transmission, electrical (gap junction) and chemical, coexist. VIIIth nerve stimulation evokes mixed (electrical and chemical) EPSPs (red trace). The trace represents the average of 20 individual responses. B, Discontinuous tetanic stimulation (trains of six pulses at 500 Hz, every 2 s for 4 min; "500 Hz protocol") of the VIIIth nerve can evoke persistent potentiation of both components of the EPSP. Plots here and in subsequent panels illustrate the amplitudes of the electrical and chemical components vs. time (each point represents the average of 20 traces) for a single experiment. C, Schematic representation of the proposed potentiating pathway. Ca^{++} entering through NMDA receptors activates CaMKII that phosphorylates either glutamate receptors and connexins or regulatory molecules. D, Repetitive stimulation of the posterior VIIIth nerve (100 Hz during 1 s.; "100 Hz protocol") evoked robust potentiation of both components of the mixed EPSP (n = 5). E, Model for endocannabinoid-mediated potentiation of electrical and chemical synaptic transmission at club endings. Synaptic activity leads to mGluR activation paired with postsynaptic membrane depolarization, triggering endocannabinoid (eCB) release from the postsynaptic Mauthner cell dendrite, which activates CB1Rs on dopaminergic fibers. CB1R activation leads to dopamine release that, by activating postsynaptic D1/5 receptors, increases PKA activity responsible for simultaneous potentiation of electrical and glutamatergic (GluR) synaptic transmission.
Panels B and C is modified from Pereda et al. [110]. Panels D and E is modified from Cachope et al. [122].

that the degree of Cx36 phosphorylation can vary locally [88]. Interestingly, a recent report suggests that the drug Modafinil, an antinarcoleptic and mood-enhancing drug, might enhance electrical coupling between inferior olivary neurons through a mechanism that requires the activation of CaMKII [124]. Thus, while GABAergic terminals originating in the deep cerebellar nuclei promote transient decoupling by shunting the non-junctional membrane at the inferior olive glomeruli [68], this

work raises the possibility that excitatory terminals of mesodiencephalic origin [67] could act to promote more lasting modifications of electrical coupling via activation of glutamate receptors (Fig. 3A). Long-term regulation of electrical coupling by nearby glutamatergic synapses contributes to coupling heterogeneity, which may represent a general property of networks of extensively coupled neurons and underlie important functions in various mammalian brain structures.
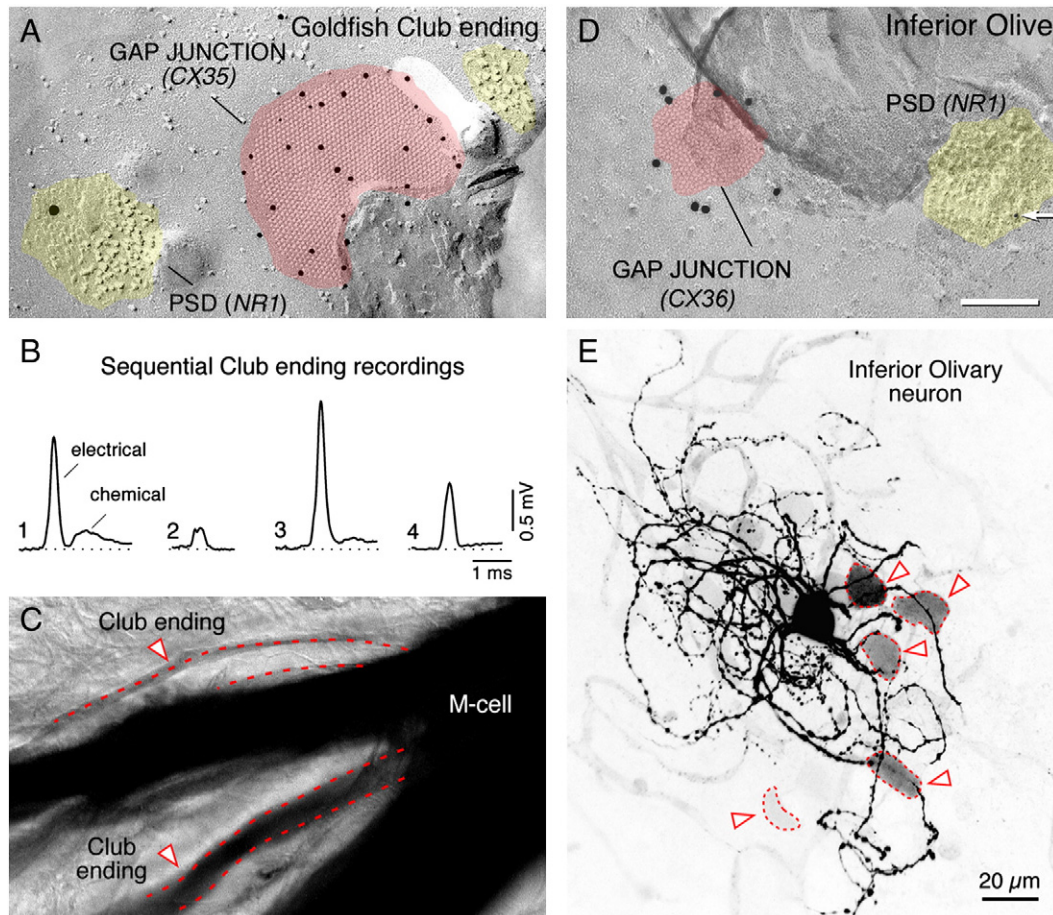
Fig. 8. Neuronal gap-junctions are in close proximity to glutamatergic synapses and show variability in coupling strength. A, Freeze-fracture immunogold labeling (FRIL) from goldfish club endings shows Cx35 (10-nm gold beads) in a gap-junction plaque (pink). A nearby aggregate of E-face particles (yellow) represents a post-synaptic density for a glutamatergic synapse and shows labeling for the NR1 subunit (18-nm gold bead), indicating the presence of an NMDA receptor. B, Unitary EPSPs measured in the same Mauthner cell dendrite, but evoked from different club endings, show variability in the electrical conductance of the synaptic transmission, even though the pre-synaptic action potentials were highly invariable (not shown). Only one of the synaptic potentials shows a clear chemical component. Thus, electrical synapses from neighboring club endings coexist at different degrees of conductance. C, Tracer coupling between the Mauthner cell (M-cell) and neighboring club endings shows a similar diversity of coupling strength. The image shows that neurobiotin injected to the Mauthner cell transferred to neighboring club endings (arrowheads) with different degrees of staining intensity, indicating that the junctions differ in their permeability. Thus, club ending synapses on the goldfish Mauthner cell coexist and different degrees of conductance (panel B) and permeability (panel C), likely because of the regulation from nearby glutamatergic synapses (panel A, Fig. 6). A similar arrangement and coexistence of variable gap-junction strengths occurs in mammals, suggesting mechanisms similar to those in goldfish may function to modulate junctional conductance in mammals. D, FRIL double labeling of Cx36 and NR1 in a rat inferior olivary neuron. The image shows a PSD (yellow) of a glutamatergic synapse with labeling for the NR1 subunit of an NMDA receptor (10 nm-gold bead). The gap-junction plaque (pink) shows labeling for Cx36 (20 nm-gold bead). This close arrangement of a Cx36-containing gap junction and an NR1-containing PSD is very similar to the close arrangement found in goldfish club endings (panel A). E, In the rat inferior olive, the labeling intensity of the somata of coupled cells (arrowheads) is highly variable. The image corresponds to a confocal projection (average of 17 z-sections) illustrating a neurobiotin-injected inferior olive neuron with multiple indirectly labeled neurons. Darker silhouettes represent more intense neurobiotin labeling; the variable labeling in the inferior olive is similar to the variable labeling of goldfish club endings (panel C).
Panel C is modified from Pereda et al. [105]. Panel E is modified from Hoge et al. [123].

Supporting the notion that activity-dependent regulation of coupling is widespread, just as in goldfish brain and inferior olive, similar E-face particles identifying active zones were close to gap junctions in rat spinal cord and retina [125], and double labeling revealed NR1 containing e-face particles and Cx36-containing gap junctions [125]. Thus, interactions may be heterosynaptic and not limited to mixed synapses, and found where glutamatergic synapses are close to gap junctions formed by a presynaptic element. Accordingly, glutamatergic transmission was also shown to promote activity-dependent long-term depression of electrical coupling between the inhibitory neurons of the rat thalamic reticular nucleus (Fig. 9). High-frequency activation of cortico-thalamic inputs triggered a long-term depression of electrical transmission between thalamic relay neurons, which required the activation of metabotropic glutamate receptors [103]. Furthermore, the activity of glutamatergic synapses was also shown to induce increase in

dye coupling between hypothalamic neurons [102]. Finally, activity-dependent depression of electrical coupling was recently observed as a result of coordinated burst firing in pairs of coupled thalamic relay neurons [126], although its mechanisms remain unknown.

3.2.3. Connexin-associated proteins and electrical synapses

In contrast to the extensive information on proteins associated with chemical synapses [127] involved in channel insertion, anchoring or removal from the plasma membrane [128–132], very few proteins have been shown to associate to the neuronal gap junctions. It is currently accepted that gap junctions are not only comprised of the defining intercellular channel proteins, but also associated scaffold and regulatory proteins [133]. Neuronal gap junctions in particular characteristically exhibit a PSD-like structure in electron microscopy, described as a "semi-dense cytoplasmatic matrix" [134], and which likely represents
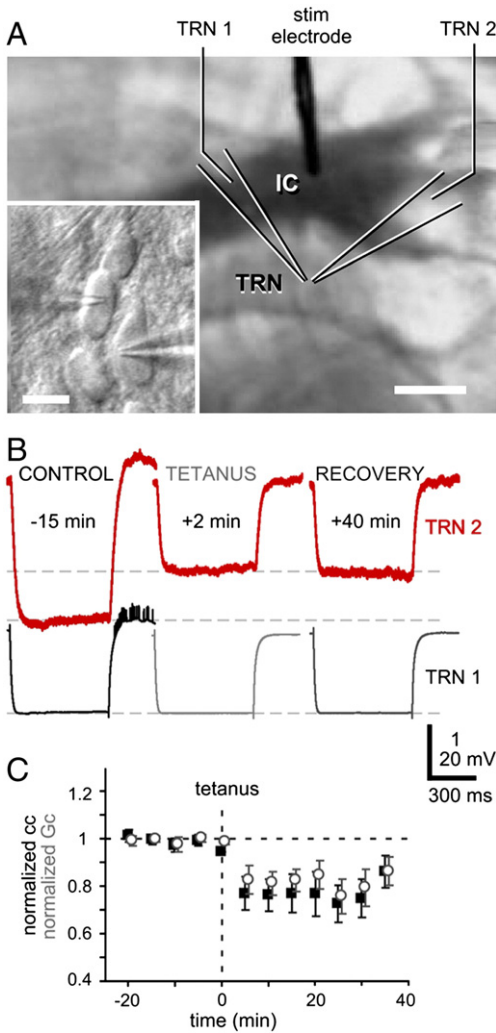
Fig. 9. Effects of high-frequency stimulation on gap junctional strength at thalamic neurons. A, IR-DIC image of a thalamocortical slice with recording arrangement. Inset: High-magnification view of recorded neurons in TRN. Scale bars indicate 1 mm and 20 μm, respectively. B, Voltage responses to hyperpolarizing current pulses in the presynaptic cell (TRN 1) and coupling responses in cell 2 (TRN 2) before and after high-frequency stimulation of cortico-thalamic glutamatergic afferents. C, Time-course of coupling coefficients (black squares) and estimated junctional conductance (gray open circles) for nine pairs of cells before and after high-frequency stimulation. The induction of long-term depression was prevented by superfusing with MCPG, an antagonist of mGLUR receptors.
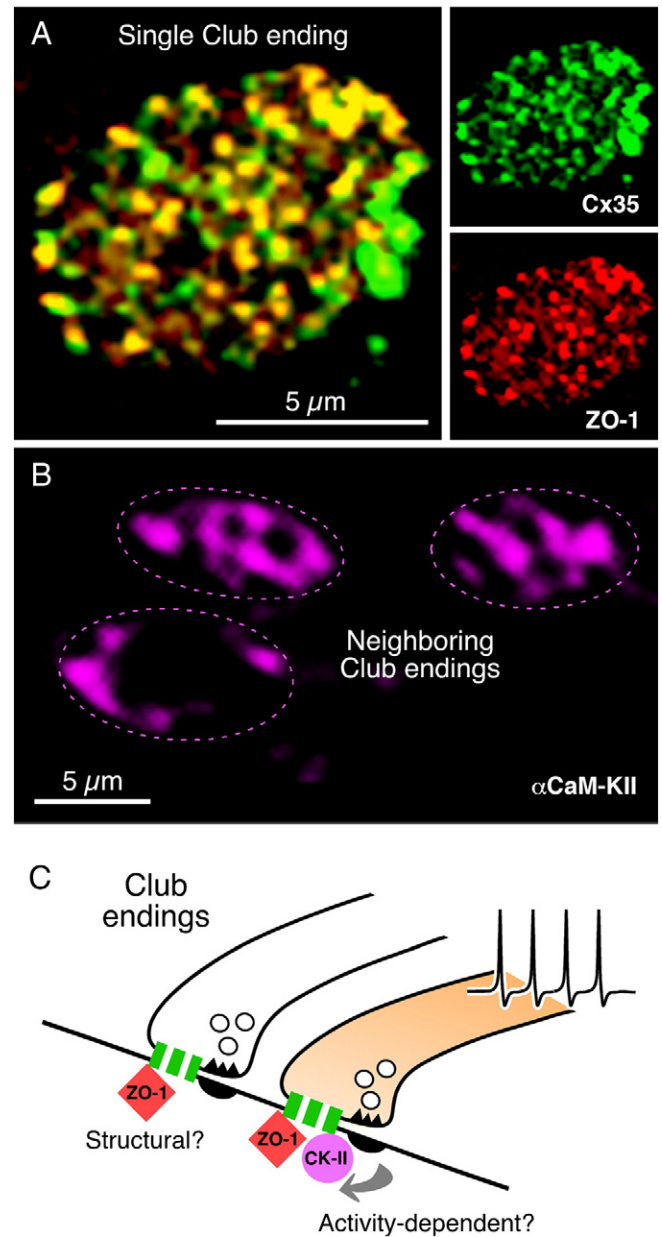Modified from Landisman and Connors [103].

Fig. 10. Connexin-associated proteins in electrical synapses. A, Cx35 and ZO-1 co-localize at club endings. Laser scanning confocal projection of an individual club ending after double immunolabeling showing intense punctate labeling for Cx35 and ZO-1 (right panels) and high levels of co-localization in yellow (left panel). B, In contrast, αCaMKII labeling is more diffuse and highly variable between contiguous club endings. While αCaMKII labeling was always observed at the periphery, where PSDs are located, it is also found at the center of the club endings contact area in some cases (compare top club endings with the bottom one). C, The extensive co-localization of Cx35 with ZO-1 suggests that this scaffold protein could constitute a structural component of gap junctions at these terminals. Activity of neighboring chemically transmitting regions within the terminal trigger changes in junctional conductance, via a PSD-mediated mechanism (arrows) promoting the association of CaMKII to Cx35 and ZO-1. The association of CaMKII to electrical synapses would be thus non-obligatory and driven by synaptic activity. For convenience, as simplified gap junction is illustrated; the cartoon does not indicate that association is exclusively pre- or postsynaptic.
Modified from Flores et al. [120].

(similar to glutamatergic PSDs) proteins associated with these intercellular channels. Cx36, the most prevalent neuronal connexin that is widely distributed throughout the mammalian brain, was shown to directly interact with two relevant proteins: zonula occludens-1 (ZO-1) [135] and CaMKII [119].

ZO-1 is a member of the MAGUK family of proteins that was reported to interact with several other connexins [133,136]. Recent work also indicates that ZO-1 also interacts with Cx35 in goldfish club endings [137]. Because its co-localization with Cx35 is extensive (Fig. 10A) [137], ZO-1 is expected to play a structural role, and the properties of the ZO-1/Cx35 association (lower affinity and faster kinetics when compared with Cx43 binding) [137] suggest the existence of a dynamic relation between these two proteins, possibly including a role of ZO-1 in regulating gap junctional conductance at these highly modifiable electrical synapses [137]. Accordingly, most recent indicates that the domain that connexin CT-domain containing the essential binding motif for interaction of Cx36 and its fish homologs is required for surface expression of these connexins at teleost [138] and mammalian

electrical synapses [139]. These interactions might contribute to regulate the turnover of gap junction channels at electrical synapses, which with an estimated half-life of 1–3 h [138], is likely to contribute to the regulation of the strength of electrical transmission [138].

Although it directly associates with Cx36 and its homologs [119,120], CaMKII might not be an obligatory component of electrical synapses. As shown in the inferior olive [119], CaMKII also associates

with Cx35 at club endings [120]. Interesting, unlike other proteins, both CaMKII labeling and distribution were highly variable between contiguous club endings (Fig. 10B), and it was not restricted to the periphery of the terminals, where glutamatergic synapses are located, but was also present at the center where gap junctions predominate. Because CaMKII characteristically undergoes activity-dependent translocation, the observed variability of labeling likely reflects physiological differences between electrical synapses of contiguous club endings, which remarkably co-exist with differing degrees of conductance [120]. That is, its presence is highly variable, even between gap junction plaques within the same contact, and likely related to differences in the degree of potentiation between individual terminals (see above). In comparison with ZO-1, which would play a more permanent or structural role, the presence of CaMKII seems to be non-obligatory and possibly regulated by neural activity (Fig. 10C). This conclusion is consistent with the dynamic translocation properties of CaMKII, whose presence is thought to represent the history of synaptic activation [120].

Thus, evidence from goldfish club endings suggest that ZO-1 and CaMKII belong to the same macromolecular complex [120] and together with other identified proteins such as zonula occludens proteins ZO-2 [140] and ZO-3 [141] and calmodulin [142], as well as those that might be identified in the future, are likely components of the "semi-dense cytoplasmatic matrix", associated with intercellular channels in neuronal gap junctions and which is likely to play a central regulatory role in electrical transmission.

4. Concluding remarks

It was generally perceived amongst neuroscientists that, in contrast to chemical transmission, electrical synapses lacked dynamic properties. Electrical synapses are considered now to be dynamic and modifiable forms of interneuronal communication. While gap junctions can also provide a conduit for small metabolites, the role of neuronal gap junctions is more often associated to providing a pathway of low resistance for the spread of ionic currents between neurons, generally referred as electrical coupling. The strength of electrical coupling is affected by gap junctional factors (gap junctional conductance) and non-junctional factors (passive and active neuronal properties). A wealth of evidence, some of which was reviewed in this article, indicates that both are targeted for regulation under various physiological situations. Gap junctional conductance was shown to be dynamically regulated by neurotransmitter modulators and the by activity of nearby glutamatergic synapses. The involvement of kinases such as PKA and CaMKII in regulating electrical transmission, which are also known to regulate the strength of chemical synapses, suggests a general role for these molecules in regulating interneuronal communication. Because gap junction regulation necessarily involves the interaction of gap junction channels with scaffold and regulatory proteins electrical synapses, as proposed for other gap junctions [133,143], should no longer be viewed as simple clusters of intercellular channels, but as complex structures in which many molecular elements participate in both short-term and long-term regulation. Plasticity of electrical transmission has also been observed at invertebrate electrical synapses [144,145], although the ultimate mechanisms underlying changes in electrical transmission remain unknown and might or might not involve changes in junctional conductance [145].

In summary, gap junctional communication between neurons has proven to be highly dynamic, a distinctive characteristic that is further emphasized by the dynamic regulation of their expression during development [146–148] and following brain injury [149,150].

Acknowledgement

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