Electrical synapses and their functional interactions with chemical synapses

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Preface

Brain function relies on the ability of neurons to communicate with each other. Interneuronal communication primarily takes place at synapses, where information from one neuron is rapidly conveyed to a second neuron. There are two main modalities of synaptic transmission: chemical and electrical. Far from functioning independently and serving unrelated functions, mounting evidence indicates that these two modalities of synaptic transmission closely interact, both during development and in the adult brain. Rather than conceiving synaptic transmission as either chemical <u>or</u> electrical, this article emphasizes the notion that synaptic transmission is both chemical <u>and</u> electrical and that interactions between these two forms of interneuronal communication might be required for normal brain development and function.

Keywords

Gap junction; Connexin; innexin; Glutamate; Mixed synapse; Development; Synaptic plasticity; Brain injury

Introduction

Communication between neurons is required for brain function and the quality of such communication is thought to underlie dynamic aspects of hardwired neural networks. Functional interactions between neurons occur at anatomically identifiable cellular regions called synapses. Although the nature of synaptic transmission has been an area of enormous controversy (See Box 1), two main modalities of synaptic transmission are now recognised: chemical and electrical. At chemical synapses, the information is transferred via the release of a neurotransmitter from one cell that is detected by an adjacent cell[1], whereas in the in the case of electrical synapses the cytoplasm of adjacent cells are directly connected by clusters of intercellular channels called gap junctions[2]. While these specializations for both forms of transmission can be found at various neuronal sites (dendrites, somata, axons), chemical transmission normally occurs between synaptic terminals along axons and the dendrite or soma of a second neuron, a muscle fiber or gland cell. The presence of these two modalities of synaptic transmission does not exclude the possibility that brain cells could also

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communicate via alternative mechanisms, such as volume transmission (diffusion through the extracellular space of neurotransmitters that reach remote target cells)[3] and by generating electrical fields that are capable of influencing the excitability of nearby neurons[4].

Box 1

Communication between neurons: the debate over the nature of synaptic transmission

Santiago Ramón y Cajal and Charles Sherrington, the fathers of modern neuroscience, established that networks of multiple elementary units or "neurons", communicate with each other via functional specializations called "synapses". Their seminal contributions were followed by a bitter debate over the nature of synaptic transmission; was it mediated by chemical or electrical signals? This controversy was known as the war of "Soup vs. Sparks"[166]. Although several researchers, most notably T.R. Elliott[167] and later Otto Loewi[168] demonstrated the existence of neurotransmitters with actions on postsynaptic cells, there was still controversy over whether transmitter release could occur in a fraction of a millisecond, the synaptic "delay" indirectly measured by Sherrington[169]. Bernard Katz and colleagues demonstrated that synaptic transmission at the frog neuromuscular junction was an electrically mediated, Ca^{++}-dependent form of transmitter release, which occurs within a fraction of a millisecond[170]. Such mechanism was showed to also occur in the central nervous system, leading to a general agreement that synaptic transmission was chemically mediated. But in 1958, David Potter communicated at a "Monday night fight" of the Marine Biological Laboratory in Woods Hole (so called because of the contentious nature of the scientific exchanges) the striking properties of synaptic transmission in crayfish, which challenged all the criteria established for chemical transmission. Postsynaptic signals reproduced the time course of presynaptic signals, transmission was bidirectional and, surprisingly, voltage-dependent. The finding provided the earliest evidence in support for the existence of electrical synaptic transmission[171] and was soon followed by seminal studies in teleost brain by Michael V.L. Bennett and colleagues[172] and David Robertson[173] and Edwin Furshpan[174], in which physiological and ultrastructural analysis were combined. Their search for the anatomical basis of electrical transmission greatly contributed to identifying the cellular structures that we know today as gap junctions. The more recent demonstration of the ubiquitous presence of electrical synapses in the mammalian brain led to the indisputable conclusion that chemical and electrical transmissions co-exist in all nervous systems.

Electrical and chemical synapses are known to coexist in most organisms and brain structures, but details of the properties and distribution of these two modalities of transmission are still emerging. Most research efforts have focused on exploring the mechanisms of chemical transmission, and significantly less is known about those underlying electrical transmission. It was thought that electrical synapses were more abundant in invertebrates and cold-blooded vertebrates and less prevalent in mammals. However, a wealth of data now indicates a widespread distribution of electrical synapses in the mammalian brain[5]. In addition to the retina, inferior olive and olfactory bulb, structures

where electrical transmission was known to occur[5], electrical synapses have been found in disparate regions of the mammalian central nervous system and shown to constitute a distinct phenotypic feature of inhibitory interneurons in general[6–8].

Perhaps because the appreciation of each form of synaptic transmission occurred in a sequential manner (at least in mammals), there is a widespread notion that electrical and chemical synapses operate independently. This article will review the evidence that chemical and electrical synapses functionally interact during development and in adulthood. Rather than being a comprehensive review of the experimental evidence, here we focus on a few examples that highlight the ability of chemical and electrical synapses to interact with each other.

Are chemical synapses more sophisticated, than electrical synapses?

From the evolutionary point of view, chemical communication between cells preceded electrical communication[9]. Communication with chemical signals occurs in unicellular organisms such as bacteria[10], mediating important phenomena such as quorum sensing[11] (the mechanism underlying detection of bacterial population density). More specific communication between individual cells requires cellular specializations between the interacting partners, a characteristic that neuronal chemical and electrical synapses inshare with immunological synapses between a lymphocyte and antigen-presenting cell.[12] From this point of view, chemical transmission requires sophisticated presynaptic molecular machinery that regulates neurotransmitter release in a probabilistic manner when an action potential invades the synaptic terminal[1] (although at some contacts, release can also be proportional to changes in resting membrane potential)[13]. A similarly complex postsynaptic molecular machinery is required, including inotropic (ligand-gated ion channels) and metabotropic receptors (G-protein coupled receptors that act indirectly through a secondary messenger) (Fig. 1a), that are capable of detecting and translating this message into various postsynaptic events, ranging from changes in resting potential ('synaptic potential') to gene expression[1]. These features allow chemical synapses to adapt to diverse functional requirements. The mechanisms and general properties of chemical synaptic transmission have been extensively reviewed [see Ref. 1 for review].

Electrical transmission is mediated by gap junctions between neurons[2], clusters of intercellular channels that directly communicate the interiors of two adjacent cells (Fig. 1b), directly allowing the bi-directional passage of electrical currents and small molecules (Ca^{++}, cAMP, IP3, amongst others). Gap junction channels are formed by the docking of two hexameric connexin 'hemichannels' or 'connexons' contributed by each of the adjacent cells[14]. Strikingly, although they assemble into almost identical structures connexons in invertebrates and vertebrates are formed by two different multigene families of proteins: connexins, which are unique to chordates, and innexins and pannexins, which are unique to invertebrates, prechordates and some chordates[2,14]. In contrast to innexins, pannexins do not seem to form intercellular channels in tissues and thus are thought to operate only as unpaired hemichannels in vertebrates[15]. Such evolutionary convergence highlights the functional relevance of gap junction intercellular communication. From a family of over 20 genes in mammals[14], only a handful of connexins were found to be expressed in vertebrate

neurons [See Ref. 15 for review][16]. Because of its widespread distribution, connexin 36 (Cx36) is considered to be the main 'synaptic' connexin[17]. Several of the 25 members of the innexin family have been identified in invertebrate neurons, mainly in fly[18], leech[19] and worm[20].

Although electrical synapses can act, to some extent, in a metabotropic fashion by allowing the passage of small metabolites, they lack the ability to amplify and transform presynaptic signals, as chemical synapses do. However, this does not mean that electrical synapses are less sophisticated; their sophistication just relies on a different functional property, their bi-directionality, which allows them to coordinate the activity of large groups of interconnected neurons[2]. Based on this bi-directional and analogic (that is, they don't require an action potential) nature, electrical synapses are especially efficient in detecting the coincidence of simultaneous subthreshold depolarizations within a group of coupled neurons, a phenomenon that increases neuronal excitability and promotes synchronous firing[21–25]. Electrical synapses are also very effective at mediating lateral excitation and increasing the sensitivity of sensory systems, such of those observed in retina[26] and primary afferents of escape networks[27–29]. Gap junction-mediated lateral excitation has also been shown to occur in a network of cerebellar interneurons, promoting the spread of chemically mediated synaptic inputs between remote dendritic arborizations[30]. Because of their reliability (transmission at electrical synapses is not probabilistic in nature) and absence of synaptic delay (transmission occurs instantaneously), electrical synapses are also a usual feature in escape response networks, in both invertebrates[29,31,32] and vertebrates[33]. Thus, from the functional point of view, no particular form of transmission is 'better' than the other one. Rather, their individual mechanisms seem to be specifically adapted to rescue and communicate different aspects of cellular processing and function.

Bolstered by the implicit molecular complexity of chemical transmission and its ability to undergo plasticity, there was until recently the widespread notion that electrical transmission is a rather simple, static and rigid form of neuronal communication. However, increasing evidence suggests that electrical synapses are structurally more complex and functionally more dynamic than previously anticipated. Far from being static, gap junctions were found to be very dynamic structures when recombinant connexins were expressed in cell expression systems and the turnover of gap junction proteins was monitored with imaging techniques[34–39]. Recent data indicate that native neuronal gap junctions are also very dynamic structures and that their channels are actively turned over[40]. More specifically, ultrastructural and functional analysis at identified mixed (electrical and chemical) synapses on the goldfish Mauthner cell (a large reticulospinal neuron in fish)[33,41] revealed that gap junction hemichannels are simultaneously added at the edges of gap junction plaques (clusters of intercellular gap junction channels) where they dock with hemichannels in the apposed membranes to form cell-cell channels and that intact junctional regions are removed from the centre of these plaques into either presynaptic axon or the postsynaptic Mauthner cell dendrite[40]. Moreover, electrical coupling was readily modified by peptides that interfere with endocytosis or exocytosis, suggesting that the strength of electrical synapses at these terminals is determined, at least in part, by a fast turnover of gap junction channels[40]. The half-life of this turnover was estimated to be 1–3 hours[40], a time consistent with that observed for other ion channels and synaptic receptors[42] indicating that this dynamic

process could be involved in regulating electrical transmission (Fig. 2). Thus, as in glutamatergic chemical synapses[43–47], regulated trafficking of connexons and intercellular channels could underlie modifications of gap junctional conductance. Furthermore, like their chemical counterparts, electrical synapses are highly modifiable by the action of neuromodulators such as dopamine and capable of activity-dependent plasticity [See Ref. 15 for review][16].

The existence of such dynamic structural and functional properties indicates that electrical transmission must rely on more than the intercellular channels. Constitutive and regulated trafficking of ligand-gated ion channels to and from the plasma membrane are important processes for the maintenance of chemical synaptic function. At glutamatergic synapses this requires interactions between the receptors' carboxy-terminals and various cytosolic proteins and scaffolding proteins[46,48,49], mostly located at the postsynaptic density (PSD)[50] (Fig. 2a). Similarly, electrical synapses require the molecular machinery to mediate the turnover of gap junction channels. Gap junctions are now considered to be part of multiprotein complexes[51–53]. Electron dense areas similar to those of PSDs, referred as "semi-dense cytoplasmic matrix"[53], have been observed at neuronal gap junctions when explored by electron microscopy (Fig. 2b). The detailed composition of these PSD-like structures is largely unknown[54], although several molecules are known to interact with Cx36[55–58] and its teleost homologs[59], most notably zonula occludens one (ZO-1)[56,57,59] and Ca^{++}/calmodulin-dependent kinase II (CaMKII)[51,52]. ZO-1 is a scaffold protein of the MAGUK family that is known to associate to many connexins[60], and that might have a similar role to PSD-95 at glutamatergic synapses[1]. Conserved regions of the carboxy-terminus of Cx36 (and its two teleost homologs)[58,59,61] mediate interactions with ZO-1 and are required for the insertion of new gap junction proteins into electrical synapses[40,61]. ZO-1 has been also proposed to have an essential role regulating the transition from connexon to intercellular gap junction channel formation in the periphery of Cx43-containing junctions[62]. In contrast to the permanent structural role of ZO-1, CaMKII has been proposed to be a non-obligatory component of electrical synapses and its association linked to synaptic activity (see below)[52]. Such regulatory associated proteins seem to be crucial for innexin-based electrical transmission as well, as the stomatin-like protein (unc-1) was shown to be required for proper channel function at gap junctions formed by UNC-9 innexin in *C. elegans*[63,64].

Recent data suggests that, similar to pre- and postsynaptic sites at chemical synapses, one side of an electrical synapse should not necessarily be considered to be the mirror image of the other[65]. Molecular asymmetries in neuronal gap junctions suggest that electrical synapses are functionally diverse. The intercellular channels at electrical synapses can in some cases be constructed by apposition of two different connexins, forming "heterotypic" (as opposed to "homotypic") gap junctions[14]. Gap junctions at auditory mixed synapses of the goldfish Mauthner cell are constructed by apposition of hemichannels formed by two homologs of mammalian Cx36[65]; while Cx35 is restricted to presynaptic hemiplaques, Cx34.7 it was found only in postsynaptic hemiplaques, forming heterotypic junctions[65]. Heterotypic gap junction channels have been associated with rectification of electrical transmission[65–68], defined as the propensity of some electrical synapses to display differential resistance to current flow in one vs. the other direction across the junction. Thus,

such molecular asymmetry can support rectification of electrical transmission which, by favoring the spread of membrane responses from the Mauthner cell to presynaptic endings, promotes cooperativity between auditory afferents. This association was initially observed in invertebrates[66] and is also supported by a wealth of work on heterotypic channels formed by recombinant connexins in cell expression systems[67–69]. Although asymmetry based on the presence of two Cx36 homologs is restricted to teleost fish (teleost fish underwent an additional genome duplication)[70], the finding provided unambiguous evidence that vertebrate electrical synapses can be asymmetric, and that such asymmetry might underlie important functional properties. Molecular asymmetry in electrical synapses might not be restricted to the existence of molecularly different connexons but could also result from posttranslational modifications of individual connexins or differences in the complement of gap junction-associated proteins forming the "semi-dense cytoplasmatic matrix"[54], endowing electrical transmission with more complex properties.

In summary, although chemical synapses seem structurally more complex and functionally dynamic, emerging evidence indicates that electrical synapses might be similarly complex, diverse and highly modifiable.

Electrical and chemical synapses interact during development

Gap junctional communication between neurons is developmentally regulated: it is initially prominent but declines at later developmental stages[71,72]. In the mammalian brain, this form of intercellular communication is widespread between postnatal days 5 and 12 and dramatically decreases after postnatal day 16 to remain restricted to some cell types[71,73–76]. The initial increase in coupling allows developing neurons to form functional domains that exhibit coordinated patterns of spontaneous activity[74,77,78]. It has been proposed that the formation of these transient domains and networks might serve as a developmental blueprint, influencing a variety of developmental cellular phenomena, ranging from cell contact inhibition, neuronal differentiation, migration, circuit formation and elimination of chemical synapses[72].

The formation of these transient gap junction networks is a common feature of invertebrate[79–82] and vertebrate[71,72,75,76] nervous systems. In *c. elegans*, a transient network formed by the innexin gap junction protein NSY-5 is required for the left and right olfactory AWC neurons to create asymmetric patterns of gene expression during embryogenesis[82]. NSY-5 mutants failed to establish this asymmetry, suggesting that intercellular communication mediated by NSY-5 junctions is a critical developmental requirement[82]. Similarly, transient gap junctions mediate avoidance of segmental homolog cell projections during development in the leech[83]. Upon contact, the processes from AP neurons, two identifiable homolog cells, stop growing and finally retract, thus defining the topography of their neuronal arbors[84–86]. Recent data suggest that transient innexin 1 (INX-1) - containing gap junctions that are formed between processes of homolog AP cells mediate this developmental phenomenon[83]. Neurite growth arrest did not occur in animals in which INX-1 was knocked down by expressing a short hair-pin interfering RNA, nor on those expressing a INX-1 mutant transgene lacking open channel pore function but that retains the adhesive cellular binding of gap junction channels[83]. These findings suggest that gap

junctions serve as conduits for an unknown messenger molecule that mediates the effect. Another well-established example of transient gap junction network occurs in the developing mammalian spinal cord[87–89]. Developing lumbar motorneurons are communicated by gap junctions, leading to synchronous patterns of nerve activity during a period in which muscle fibers are innervated by axons originating from multiple motorneurons[87,89]. The transition from multiple innervation to the characteristic single innervation in muscle fibers occurs at late embryonic and early postnatal stages and is an activity-dependent process, which results from competition between active synapses[90]. It was shown that a transient gap-junction network modulates this developmental transition from multiple to single fiber innervation[91]. Gap junctional coupling between motorneurons disappears at late embryonic and early postnatal stages causing lack of correlated activity between innervating axons (elimination cannot occur if synapses are synchronously activated), which in turn paves the way for synapse competition and subsequent synapse elimination in multiply innervated muscle fibers[91]. Reduction of gap junctional communication with gap junction blocking agents disrupted synchronous patterns of nerve activity and enhanced synapse elimination[91]. Consistent with this finding, acceleration of synapse elimination was observed in Cx40 KO mice[92], a connexin that is expressed in developing motorneurons and that dramatically decreases after birth[87], indicating a primary role for transient gap junction networks in gating the transition from multiple to single fiber muscle innervation.

Remarkably, the formation and subsequent elimination of gap junction coupling between neurons was found to be correlated with the emergence of chemical neurotransmission in several species. This robust phenomenon was again observed at developing invertebrate[79,93,94] and vertebrate nervous systems[95–97]. Furthermore, several studies indicate that gap junction proteins expressed during development are required for the formation of chemical synapses. Flies containing mutations in the innexin genes *Shaking B* and *Ogre* failed to establish appropriate functional synaptic connections in the visual system of this organism, as evidenced by the absence or alterations in the electroretinogram[98]. This developmental defect could be rescued by transgenic expression of the lost innexins during pulpal development, but not at later stages[98]. More direct evidence of the relationship between electrical synapses and the formation of chemical synapses was observed at identifiable motorneurons of the snail *Helisoma*[93]. Manipulations that led to a reduction of coupling between these snail motorneurons accelerated the formation of chemical synapses, whereas, exposure to cholinergic antagonists (which block chemical neurotransmission at these synapses) caused prolonged maintenance of electrical transmission[93], suggesting an inverse relationship between the establishment of chemical and electrical connectivity at early stages of synaptic development. Such relationship between the formation of electrical and chemical synapses was also observed in vertebrates. The presence of gap junction coupling between developing spinal motorneurons also followed an inverse relationship with the formation of chemical synapses[95]. The decline in motorneuron coupling that occurs at late embryonic and early postnatal age is correlated with the formation of glutamatergic synapses in these spinal circuits[95]. Furthermore, exposure to NMDA receptor antagonists arrested the developmental decline in gap junction coupling between spinal motorneurons, suggesting that the increase in glutamatergic synaptic activity that is generally associated

with the onset of locomotion promotes the disappearance of gap junction-mediated networks between developing motorneurons[95]. The exquisite relationship between the early presence of electrical connections and the subsequent formation of chemical synapses has recently been demonstrated in the leech. The sequential development of electrical and chemical synapses between two types of identifiable neurons that participate in a behaviorally relevant local-bending circuit offered the possibility of directly addressing this issue[79]. Synaptic transmission between the P cell (that transduces pressure) and AP cell (a motorneuron-like cell) is initially exclusively electrical and becomes predominantly chemical in the adult animal. Although electrical transmission remains, it is considerably weakened[94]. Silencing INX-1 in embryonic P cells when innexin-based gap junctions are initially forming and chemical synapses are absent (~50% embryonic development), prevented not only the establishment of electrical synapses but also the development of chemical transmission[94] (Fig. 3a), elegantly demonstrating the requirement of electrical synapses for the formation of chemical contacts. Moreover, the development of networks mediated by chemical synapses in the mouse olfactory bulb was arrested in Cx36 knockout mice[96] in which electrical transmission is greatly reduced, indicating that the early presence of electrical synapses is also a prerequisite for the formation of chemical synapses in mammals. This phenomenon was also observed in the developing neocortex. Consecutive divisions of individual radial glial progenitor cells normally produce sister excitatory neurons that lead to the formation of ontogenetic cortical columns that preferentially develop specific chemical synapses with each other rather than with nearby non-siblings[97]. Sister excitatory neurons are initially electrically coupled[97] and blockade of this communication impairs the subsequent formation of specific chemical synapses between sister excitatory neurons in ontogenetic cortical columns[97].

We have discussed the mechanistic relationship between the presence of electrical synapses and the subsequent formation of chemical connections. However, conversely, receptors for chemical neurotransmitters and chemical synapses have been shown to regulate the emergence and disappearance of gap junctions during development[99–101]. *In-vitro* studies of cortical and hypothalamic neurons indicate that, despite that chemical connections are not yet formed, activation of specific receptors for chemical neurotransmitters regulate the expression of Cx36 at early developmental stages[100]. Prolonged (two weeks)[100] activation of group II metabotropic glutamate receptors (mGluRs) leads to an increase in the expression of Cx36 via a cAMP/PKA dependent intracellular pathway, whereas activation of type A GABA receptors (GABA$_A$Rs) leads to a reduction of Cx36 expression[100] (Fig. 3b), indicating that the formation of gap junctional networks relies on the interplay between these two types of receptors. Because GABA$_A$Rs are depolarizing at these early developmental stages, their effects are mediated via Ca^{++} influx and activation of PKC[100]. This developmental regulation of Cx36 gene expression involves regulation of both gene transcription (mGluR-dependent increase) and protein translation (GABA$_A$R-dependent decrease)[100]. These changes are thought to be specific for these receptors[100].

Activation of glutamate receptors also reduces coupling observed at late developmental stages and as mentioned blocking NMDA receptors delayed the formation of chemical synapses in spinal motorneurons[95], suggesting that the emergence of glutamatergic

transmission regulates uncoupling. This is supported by findings in the rat hypothalamus[99]. Activation of NMDA receptors at late developmental stages led to $Ca^{++}/cAMP$ response element binding protein (CREB)-dependent down regulation of Cx36 gene expression[99], providing a direct mechanistic relationship between the emergence of chemical transmission and the disappearance of neuronal gap junction coupling (Fig. 3b).

In summary, the development of neural circuits in disparate nervous systems seems to critically rely on interactions between chemical and electrical synapses, which reciprocally and dynamically regulate the emergence of these two forms of transmission (Fig. 3c).

Electrical and chemical synapses interact in the adult nervous system

The effects of a special type of neurotransmitters: neuromodulators on gap junction communication represent a clear example of the interactions between chemical and electrical transmission in the adult nervous system. Neuromodulators are released from presynaptic terminals and activate specific metabotropic G-protein coupled receptors which trigger signaling cascades that modulate synaptic communication between target cells (Fig. 4a). Dopamine for example, has been shown to modulate gap junction communication at various vertebrate and invertebrate cell types [See Refs. 16 and 102 for review][16,102], suggesting that both connexin and innexin gap junction proteins are targets of its regulatory actions. At electrical synapses mediated by Cx36 or Cx57, and its teleost homologs, activation of dopamine can lead to either an increase or a decrease of gap junctional conductance between neurons via a cAMP-dependent mechanism that involves the activation of PKA. That is, dopamine was observed to enhance coupling at goldfish electrical synapses[103,104] and to promote decoupling of between retinal horizontal cells[105,106,107]. Two phosphorylation sites in Cx36 and its fish homologs, Ser110 and Ser293 (Ser276 in teleost)[107,108], seem to be essential for the effects of dopamine on electrical synapses. Recent evidence indicates that dopamine acting via D1/5 receptors, can either promote PKA-mediated phosphorylation of Cx36 at regulatory sites, leading to an increase in coupling, or to decoupling via PKA-activation of protein phosphatase 2A and subsequent de-phosphorylation of Cx36[109], thus providing a mechanism for bi-directional regulation of synaptic strength. Dopamine can also act via activation of D2 receptors, which leads to a reduction of cAMP and PKA activation, and increases coupling between rods and cones in vertebrate retina[110]. Other neuromodulatory systems that regulate the strength of electrical synapses include noradrenaline[111], serotonin[112,113], histamine[114] and nitric oxide[115,116].

Regulation of electrical coupling by neuromodulators can have profound functional consequences. Chemical and electrical synapses co-exist at various circuits raising the question of how these two networks interact to generate function[117]. In the rabbit retina rod and cone inputs were shown to converge on cone bipolar cells[102]. In the case of the cones, the connection is direct via ON bipolar cells, whereas for the rods, the connection is indirect. This indirect connection specifically relies on electrical synapses between AII type amacrine cells themselves and ON bipolar cells[118]. Both homologous and heterologous synapses are regulated by dopamine (AII to AII gap junctions) and nitric oxide (AII to On bipolar gap junctions), which efficiently reconfigure retinal circuits by switching between direct and indirect pathways[118,119].

Remarkably, it has been shown that fast, amino acid-mediated, chemical transmission also interacts with electrical synapses. "Mixed" chemical and electrical synapses found at "Large Myelinated Club endings", or simply "Club endings"[120] -- terminations of primary auditory afferents on the teleost Mauthner cells -- provide a unique opportunity to study interactions between these two modalities of synaptic transmission (Fig. 4b)[120][121]. Activation of these synapses with high-frequency bursts (500 Hz) of activity leads to long lasting potentiation of both the electrical and glutamatergic components of the mixed synaptic potential evoked by the activation of these terminals[122,123]. Thus, both forms of transmission at these contacts exhibit activity-dependent plasticity. Strikingly, potentiation of both electrical and chemical transmission were blocked by NMDAR antagonists[122,123], suggesting that potentiation of electrical transmission is initiated by the activity of the coexisting glutamatergic synapses. The potentiations also required of an increase in postsynaptic Ca^{++} and the activation of CaMKII[124] (Fig. 4b). CaMKII activation was shown to lead to an increase in gap junction conductance not only at goldfish Club endings, but also in Cx36-containing gap junctions and cell expression systems[125]. Consistent with these findings, CaMKII was found to phosphorylate Cx36 at retinal electrical synapses at sites that enhance coupling between these cells[126]. CaMKII is an abundant component of the PSD at chemical synapses and has been implicated in mechanisms of activity-dependent plasticity at chemical synapses[50,127]. In similarity to its interaction with the NR2B subunit of the NMDAR at PSDs, CaMKII interacts with Cx36 by binding to its cytoplasmic domains[51,127]. There are multiple phosphorylation sites in Cx36 and its fish homologs Cx35 and Cx34.7 for the alpha subunit of CaMKII[51,52]. Residues S315/ S298/ S300 in Cx36, Cx35 and Cx34.7, respectively, constitute exclusive phosphorylation sites for CaMKII that are not shared with other kinases[51,52]. In contrast, residues S110 and S293 in Cx36, S110 and S276 in Cx35, and S110 and S277 in Cx34.7, are shared with PKA[51,52].

Mixed synapses provided unambiguous evidence that glutamatergic and electrical synapses interact. Because interactions occur postsynaptically (Fig. 4b), it is possible that that similar interactions could also take place heterosynaptically, between neighboring glutamatergic and electrical synapses (Fig. 4c). Supporting this possibility, ultrastructural evidence shows the proximity of NR1-containing PSDs to gap junctions in the rat inferior olive and retina, at distances that comparable to those observed in goldfish Club endings[128,129]. Indeed NMDAR/CaMKII-dependent modulation of gap junction coupling was proposed to take place in the inferior olive[128,130] and shown more recently to occur in the retina[126]. That is, presynaptic activity of glutamatergic ON bipolar cells increases phosphorylation of Cx36 in amacrine AII cells[126]. Glutamatergic synapses were also shown to induce an increase in dye coupling between hypothalamic neurons[131]. Moreover, glutamatergic transmission was shown to promote activity-dependent long-term depression of electrical coupling, indicating that interactions between glutamatergic and electrical synapses are diverse and widespread. 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[132].

Interestingly, the interactions between chemical and electrical synapses were Club ending-specific and did not spread to neighboring Club endings[133], suggesting that the mechanisms of PSD-initiated interactions with gap junctions are short-ranged and take place within less

than 5 microns, the usual distance from two neighboring Club endings in the smooth Mauthner cell dendrite. Given that plastic changes triggered by glutamate are terminal specific and Club ending afferents can be differentially activated by sounds, the gap junctions at these contacts co-exist at different degrees of conductance on the Mauthner cell dendrite[133] These findings suggest that a single cell can be differentially coupled to its neighbours based on the activity of chemical synapses located in the proximity of each gap junction. Inferior olivary cells, which connect to up to 40 other inferior olivary cells, have been shown to be differentially coupled with its partners. Such heterogeinity in coupling strength has also been reported in the, rabbit retina[109], and rat cerebellar cortex[134]. In summary, by regulating nearby gap junctions, PSDs at glutamatergic synapses provide a mechanism for fine tuning electrical coupling within networks of electrically coupled neurons. This form of regulation can reconfigure networks and create functional compartments of neurons with propensity to cooperate, by determining the probability with which neurons interact with each other.

Heterosynaptic interactions between electrical and chemical synapses can be very complex and both involve intricate interactions between glutamatergic synapses and neurotransmitter modulators. High frequency stimulation of Club endings potentiates both electrical and chemical transmission. This effect is dependent on the activation of mGLUR-1 receptors[135] and the formation of endocannabinoids, which by acting on cannabinoid type-1 receptors (CB1R) lead to the release of dopamine from varicosities located in the close vicinity of the Club endings and Mauthner cell dendrites[135]. The release of dopamine from nearby varicosities in turn leads to the potentiation of the electrical (and glutamatergic) synaptic response via a cAMP/PKA-mediated postsynaptic mechanism[135] (Fig. 4d). This mechanism of potentiation clearly illustrates the complexity and possibilities of interactions between chemical and electrical synapses. It also demonstrates that the local availability of dopamine is not exclusively under the control of dopaminergic neurons, but that it is also determined by local synaptic activity (both electrical and chemical).

Finally, the "shunting" effect of inhibitory synapses provides another example of interactions between chemical and electrical synapses[136–138]. Chemical inhibitory synaptic conductance often short-circuits the currents that are generated at adjacent excitatory synapses by locally increasing membrane conductance[136,138]. Depending on the anatomical arrangement, inhibitory conductances can dramatically reduce coupling if they are in the proximity of electrical synapses by "shunting" electrical currents, before they have had the chance to spread to a nearby neuron through the gap junctions (Fig. 5). [See Ref. 15 for review][16] This form of interaction was shown to occur within the inferior olive glomerulus[136,137] and between expansion motorneurons of the mollusk *Navanax*[138], where quick and transient decoupling sculpts clusters of functionally related neurons involved in phasic behaviors. Further emphasizing the functional significance of these fast interactions, reciprocal electrical and inhibitory synapses organize networks of mammalian GABAergic interneurons[139]. Modeling one of these interneuron networks in the cerebellum suggested that combining fast inhibitory synapses and electrical coupling can promote synchronized gamma oscillations[139], which have been associated with cognitive processing and are affected in some pathological conditions[140].

Are interactions between electrical and chemical synapses involved in brain dysfunction?

The strong developmental interrelationship between electrical and chemical synapses suggests that its disruption might underlie neurological conditions that are acquired during development. Lack or dysfunction of electrical transmission could lead, as shown in neocortex[97] and the Cx36 KO mice[96], to subtle deficits in the formation of mature neural circuits that may cause or contribute to neurological or behavioral conditions. Interestingly, the Cx36 gene has been associated with juvenile myoclonic epilepsy, a generalized form of epilepsy with onset in early adolescence[141,142] but the exact mechanistic linkage remains unknown. It has been suggested that some single nucleotide polymorphisms may influence Cx36 gene expression and contribute to the pathogenesis of this disease by affecting the normal formation of neural circuits[141]. In addition, dysfunction of glutamatergic transmission, which via NMDAR activation triggers the developmental decline in gap junctional communication[99], could result in abnormal levels of electrical coupling in some brain regions that might lead to increased neuronal synchrony and seizures[143].

As previously mentioned, Cx36-mediated electrical synapses are a feature of inhibitory interneurons in the adult mammalian brain, including neo-cortex, thalamus and hippocampus[6–8,132]. Inhibitory interneurons are crucial for various brain processes, as they contribute to the generation of gamma-frequency oscillatory activity (30–80 Hz), which has been associated with cognitive processing[140,144]. High-frequency network oscillatory synchronizations appear to be crucial in defining the conscious state[145], and for "associative binding" for learning and memory. Strikingly, these cortical gamma oscillations are impaired in Cx36 knockout mice[146] suggesting a role for electrical synapses in generating this rhythm. Alteration of oscillatory activity has been proposed to contribute to the pathophysiology of schizophrenia[144,147], Parkinson's disease[148] and autism spectral disorders[149]. Moreover, dysfunction of glutamatergic[150–152] and dopaminergic[153,154] transmissions, are involved in these conditions, suggesting that dysregulation of electrical coupling could contribute to the underlying pathophysiological processes. The investigation of these possibilities could lead to the identification of novel therapeutic opportunities for treating these conditions.

Recent data suggest that the interactions between chemical and electrical synapses that are observed during development have an important functional role after brain insult. Strikingly, networks of electrically coupled neurons identified during development can reappear after brain injury. Adult cat spinal motorneurons become re-coupled by gap junctions after peripheral nerve injury[155], reestablishing the transient gap junction network observed during development. Gap junction coupling was proposed to play a beneficial functional role by helping to maintain the viability of axotomized motorneurons until synaptic connections with their muscle fiber targets are reestablished[155]. Although it is unclear if this axotomy-induced spinal network disappears after nerve regeneration, glutamatergic transmission was shown to increase expression of Cx36 and gap junction communication in in-vivo and in-vitro models of ischemic stroke and traumatic brain injury[101]. The increase in Cx36 expression occurs about 2 hours after injury and is likely to be triggered by the massive

release of glutamate from injured neurons[101]. As observed during development[100], activation of group II mGluRs was also shown to mediate this increase in gap junction communication[156].

These interactions between glutamatergic and electrical transmission are thought to control death and survival mechanisms in injured neurons[156]. A wealth of data indicate that activation of NMDA receptors mediate the glutamate toxicity that occurs in the injured brain[157]. Interestingly, electrical synapses seem to be involved in this phenomenon. The death of forebrain neurons evoked by intraperitoneal injection of NMDA was greatly attenuated by gap junction blockers and in Cx36 KO mice[158,159], suggesting that gap junctional coupling could have a deleterious effect for neuronal survival. It has been suggested that neurodegenerative signals could be passed to other and undamaged neurons (neurons adjacent to the lesion or "penumbra" area) as a result of the increase in neuronal coupling triggered by the activation of group II mGluRs[160] (Fig. 6a).

Conclusions

Electrical synapses have proven to be more widespread in the mammalian brain than originally anticipated. Thus, networks of electrically and chemically coupled neurons are not restricted to invertebrates but seem to be a feature of all nervous systems. Such realization emphasizes the need to further explore the functional properties of electrical synapses (of which we know significantly less) as well, based on the evidence reviewed here, their interactions with chemical synapses.

Mixed synapses provide unambiguous evidence that rather than unconnected lines of communication electrical and chemical synapses cooperate and extensively interact, and that the speed and reliability of electrical transmission can be combined with the ability to induce plastic changes that is characteristic of chemical transmission. Mixed synapses are widespread in cold-blooded vertebrates[120] but they seem to be less numerous in mammals, perhaps because of the much-improved speed of transmission observed at mammalian chemical synapses[161]. However, there is growing evidence of their presence in the mammalian nervous system including the spinal cord[162], a subset of hippocampal mossy fibers[163,164], and, interestingly, between dendrites of hippocampal inhibitory interneurons[165].

Interactions between electrical and chemical synapses are complex and diverse, and occur at all stages of brain development. While during development interactions between electrical synapses are critical for the formation on neural circuits, interactions in the adult brain result in dynamic reconfiguration of hardwired networks. These interactions are likely to have important pathological implications (Fig. 6b). Recapitulation of some developmental interactions between chemical and electrical synapses after brain injury indicates that, rather than exceptional, these interactions constitute basic and necessary mechanisms of communication in the nervous system. Furthermore, the interactions between dopaminergic, glutamatergic and electrical synapses that have been observed in the adult brain highlight their importance for reconfiguring neural circuits and their dysregulation could contribute to cognitive impairment. Future studies are likely to confirm the intimate relationship between

these two modalities of synaptic transmission and shed further light on their contribution to disease states.

Acknowledgments

Glossary terms

Lateral excitation	The term lateral inhibition refers to the ability of an excited neuron to inhibit or reduce the activity of its neighbors. Lateral inhibition following activation of a sensory afferent is thought to increase spatiotemporal perceptual discrimination. Lateral excitation, a less appreciated property of sensory and cortical networks, refers to the ability of an excited neuron (or sensory afferent) to excite its neighbors. While reducing discrimination, lateral excitation greatly enhances input sensitivity
Escape networks	Neural networks found in invertebrate and vertebrate nervous systems that seem optimized to mediate fast escape behaviors. They usually contain a small number of cells and include sensory and motor neurons
Mauthner cell	The Mauthner cells are two large reticulospinal neurons found in teleost fishes that mediate (amongst other functions) tail-flip sensory evoked escape responses
Postsynaptic density (PSD)	Originally named after its identification by electron microscopy, the term refers to a macromolecular complex that supports postsynaptic function at chemical synapses. Better characterized at glutamatergic synapses, the PSD is formed by a large number of proteins that include neurotransmitters receptors, scaffolding proteins and regulatory signaling molecules
Electroretinogram	Extracellularly recorded electrical response that reflects the activation of various cells in the retina (including photoreceptors, inner retinal cells, and the output ganglion cells) in response to visual stimulation
ON bipolar cells	Retinal cell that functionally link photoreceptors (cones and rods) with ganglion cells. ON bipolar cells are excited by the release of glutamate from photoreceptors while OFF bipolar cells are instead inhibited
All type amacrine cells	Amacrine cells represent a class of retinal interneurons that represent the main input to ganglion cells, the output neuron of the retina. Amacrine cells also regulate bipolar cells, which represent the other source of input to ganglion cells. The AII is a

type of amacrine cell that relays rod-driven information through the ON-center cone bipolar axons to ON-center ganglion cells via electrical synapses

Associative binding   The term refers to tasks of episodic memory that require the associative binding of distinct components into a compound episode. They commonly include the binding of two items or a single item with a specific context

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Biography

Alberto Pereda is a Professor of Neuroscience at the Albert Einstein College of Medicine (Bronx, New York). His postdoctoral training focused on investigating mechanisms of postural control during sleep (with Michael Chase and Francisco Morales at UCLA) and the plastic properties of auditory synapses on the goldfish Mauthner cells (with Donald Faber at the University at Buffalo). His current research efforts are centered on investigating the properties and mechanisms of plasticity of gap junction-mediated electrical synapses in the vertebrate brain.

At-a-glance Summary

1. There are two main modalities of synaptic transmission: chemical and electrical. Although chemical synapses are perceived as structurally more complex and functionally dynamic, emerging evidence indicates that electrical synapses might be similarly complex, functionally diverse and highly modifiable.

2. Far from functioning independently and serving unrelated functions, these two modalities of synaptic transmission closely interact. Rather than conceiving synaptic transmission as either chemical _or_ electrical, this article emphasizes the notion that synaptic transmission is both chemical _and_ electrical and that interactions between these two forms of interneuronal communication are required for normal brain development and function.

3. The development of neural circuits in disparate nervous systems (both vertebrate and invertebrate) seems to critically rely on interactions between chemical and electrical synapses, which reciprocally and dynamically regulate the emergence of these two forms of transmission.

4. While during development interactions between electrical synapses are critical for the formation on neural circuits, interactions in the adult brain result in dynamic reconfiguration of hardwired networks. The strength of electrical synapses is regulated by neurotransmitters modulators such as dopamine and by glutamatergic synapses in an activity-dependent fashion.

5. Interactions between electrical and chemical synapses are also likely to have important pathological implications. Recapitulation of developmental interactions between chemical and electrical synapses was observed after brain injury and dysregulation of electrical synapses by neurotransmitters could contribute to cognitive impairment.
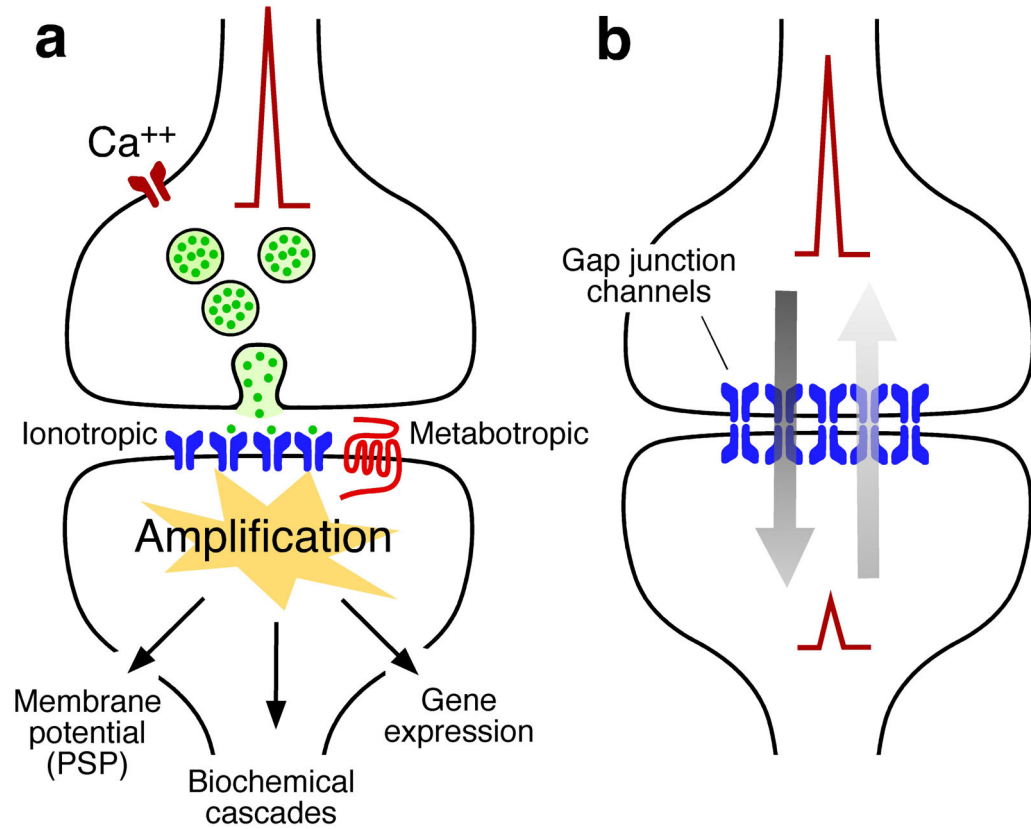
Figure 1. The two main modalities of synaptic transmission
a, Chemical transmission requires sophisticated presynaptic molecular machinery that regulates neurotransmitter release in a probabilistic manner upon depolarization of the presynaptic terminal, in this case by the arrival of an action potential. A similarly complex postsynaptic molecular machinery is also required. This includes the presence of inotropic and metabotropic receptors that are capable of detecting and translating the presynaptic message (neurotransmitter) into various postsynaptic events, ranging from changes in resting potential to gene expression. **b**, Electrical transmission is mediated by clusters of intercellular channels called gap junctions that communicate the interior of two adjacent cells, directly allowing the bi-directional passage of electrical currents carried by ions (arrows), as well intracellular messengers and small metabolites (not illustrated here). Electrical synapses are bi-directional in nature: when a "presynaptic" action potential propagates to the "postsynaptic" cell, the membrane resting potential of the "postsynaptic" cell simultaneously propagates to the "presynaptic" cell (arrows).
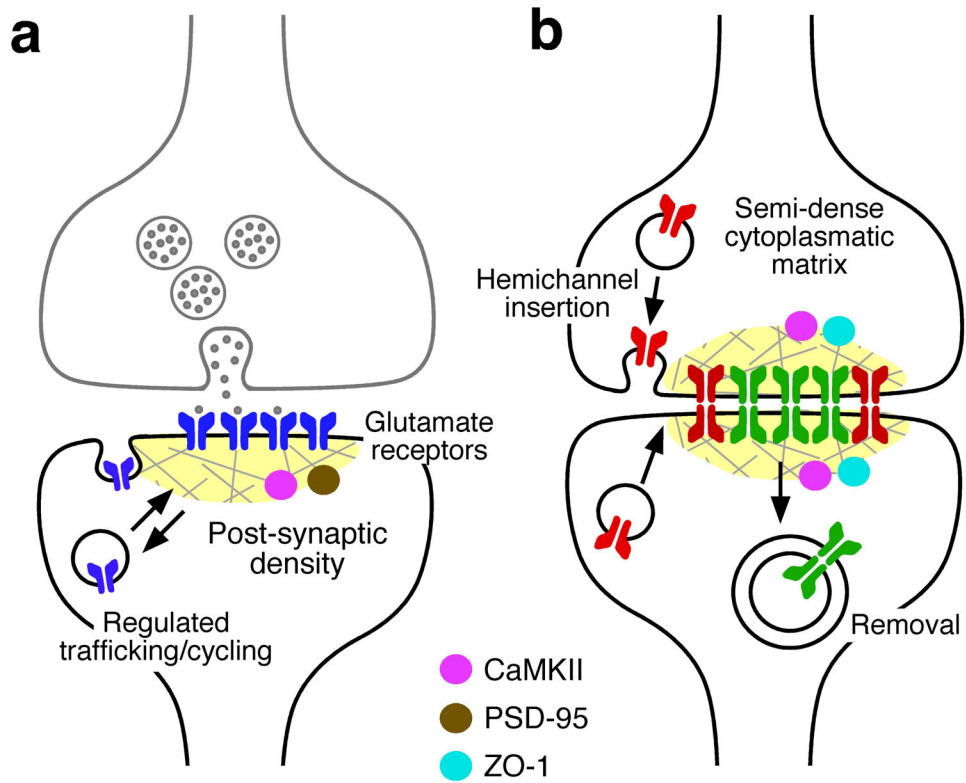
Figure 2. Trafficking of channels at chemical and electrical synapses
a, Glutamate receptors are trafficked in and out of synapses. Postsynaptic densities provide a scaffold that helps to regulation this trafficking. PSD-95 and CaMKII are both abundant components of postsynaptic densities. Regulated trafficking of AMPA receptors (blue) is thought to underlie the modification of synaptic strength at glutamatergic synapses. **b**, Gap junction channels at electrical synapses turnover. New connexons are trafficked to the membrane in vesicles as unpaired hemichannels, where they are inserted at the periphery of the gap junction plaque and dock with hemichannels in the apposed membrane. They are internalized as small clusters of entire channels (green) into either of the coupled cells from regions near the center of the plaque. Proteins in the "semi dense cytoplasmatic matrix" act as scaffold. ZO-1 is a structural component whereas CaMKII seems to be a non-obligatory component of the macromolecular complex with functions that might be similar to those at postsynaptic densities of chemical synapses.
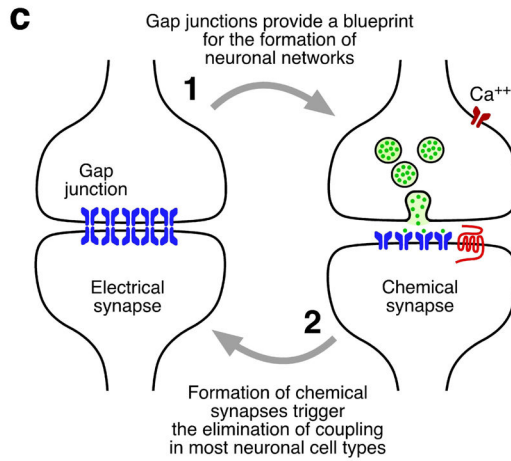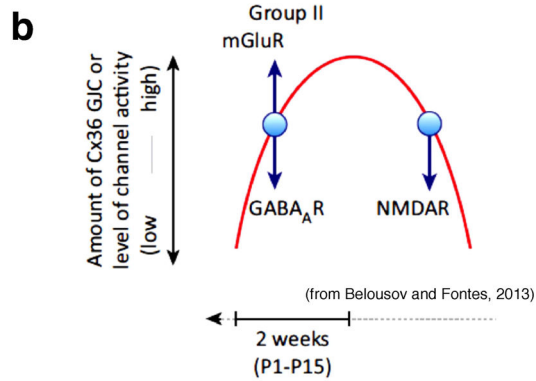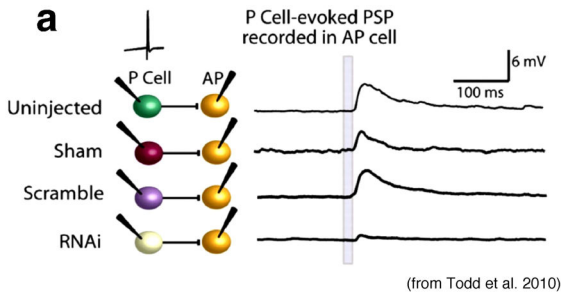
Figure 3. Electrical and chemical synapses interact during development

a, Blockade of electrical synapse formation in leech embryos perturbs the formation of chemical synapses. Chemical synaptic potentials in an AP cell in response to a single spike in a P cell (marked by the gray bar on the AP recordings) under control conditions (uninjected, sham, scrambled) and after injection of double-stranded RNA (RNAi) that interferes with the translation of INX-1 in embryonic P cells, at a developmental time (~50% embryonic development) at which innexin-based gap junctions are forming but chemical synapses have not yet formed. [Data from Todd et al., 2010 (figure will be redrawn by the journal's graphic art department).] **b**, Effect of signaling through GABAA receptor (GABAAR), metabotropic glutamate receptor mGluR) and NMDA receptor (NMDAR) on gap junction communication during development. Red line represents the increase (upward phase) and decrease (downward phase) in the amount of neuronal gap junction

communication (GJC) and expression of connexin 36 (Cx36) during development. Blue arrows show the direction of the change in gap junction communication after activation of the receptor. P1 and P15 indicate postnatal days 1 and 15. [Taken from Belousov and Fontes et al., 2013 (figure will be redrawn by the journal's graphic art department)] **c**, Modalities of interactions between electrical and chemical synapses during development.
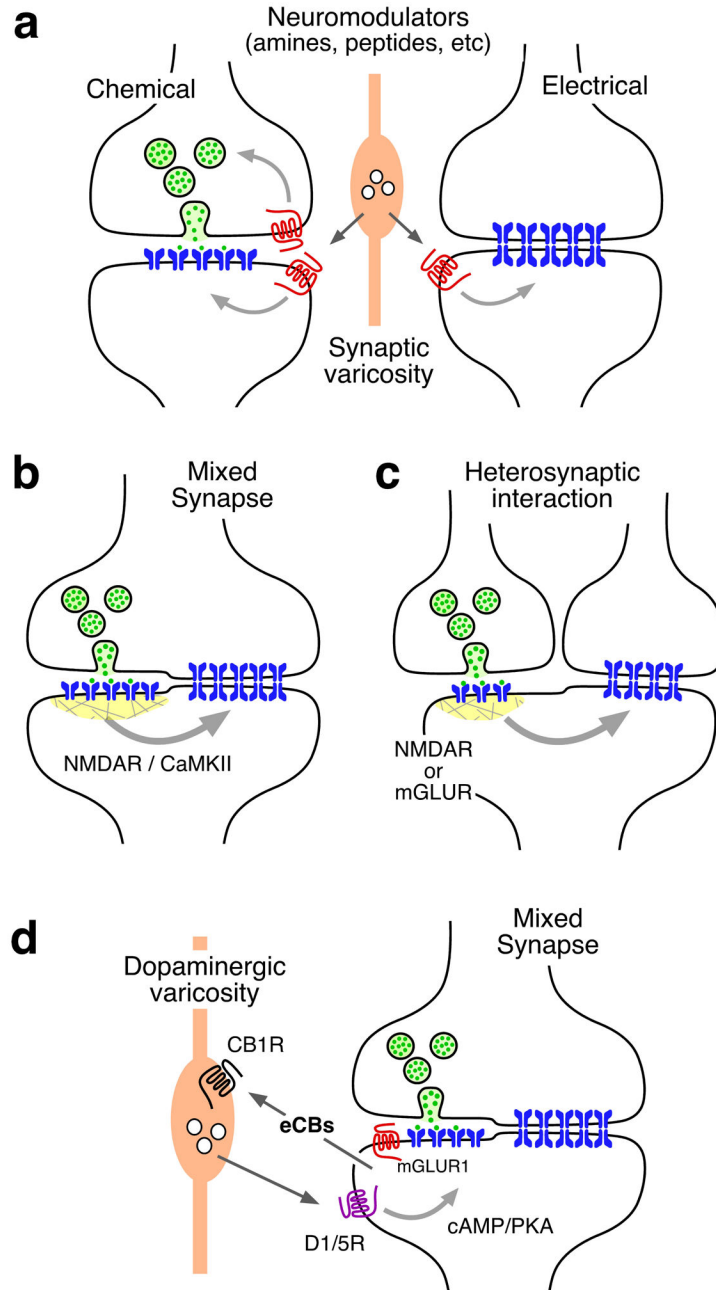
Figure 4. Modalities of interactions between electrical and chemical synapses in the adult nervous system

a, Neurotransmitter modulators released by nearby synaptic terminals (orange) regulate the synaptic strength of chemical and electrical synapses via activation of G-protein coupled metabotropic receptors. Regulation at chemical synapses could occur pre- or postsynaptically. **b**, Electrical and chemical synapses co-exist at mixed synapses. Glutamatergic synapses regulate the strength of electrical synapses via a postsynaptic mechanism that includes the activation of NMDA receptors (NMDAR) and CaMKII. **c**, Regulation of electrical synapses by glutamatergic transmission could also be heterosynaptic. Nearby glutamatergic synapses can regulate electrical transmission via

NMDAR or mGLUR activation. **d**, Another mechanism of interaction at goldfish mixed synapses results when synaptic activity leads to mGluR activation, which in turn triggers endocannabinoid (eCB) release from the postsynaptic cell, and activates cannabinoid type-1 receptors (CB1Rs) on nearby dopaminergic fibers. CB1R activation leads to dopamine release that, by activating postsynaptic dopamine D1/5 receptors (D1/5R) and increasing PKA activity, is responsible for simultaneous enhancement of electrical and glutamatergic synaptic transmission.
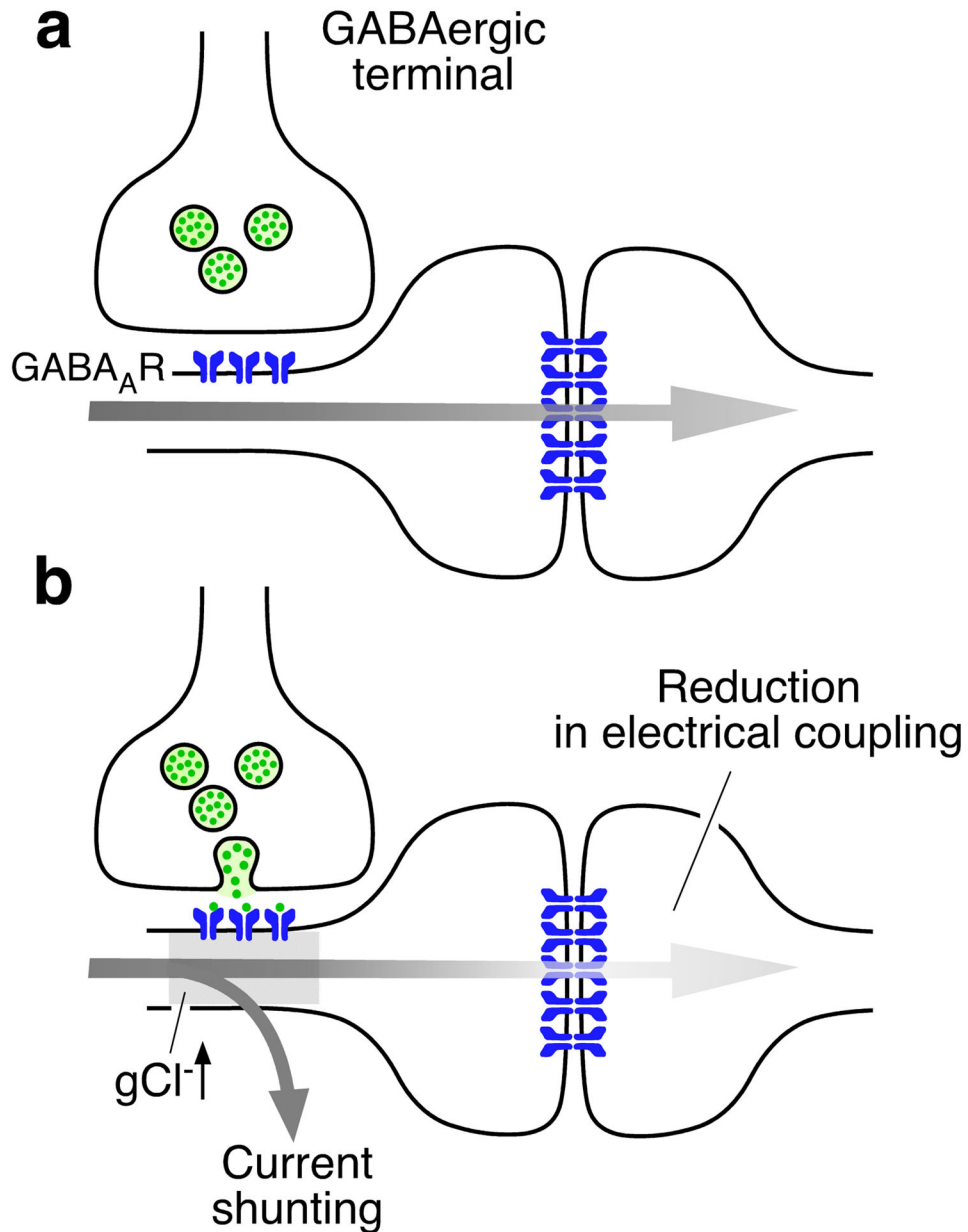
Figure 5. Interactions between electrical synapses and inhibitory chemical synapses
a, Inhibitory GABAergic synapses are often located in the vicinity of gap-junctions between dendro-dendritic processes (spines) of two neurons. **b**, By locally increasing membrane conductance, inhibitory synaptic chloride conductances (gCl^-) produced by activation of GABARs briefly shunt excitatory currents to temporarily reduce effective electrical coupling between two coupled neurons.
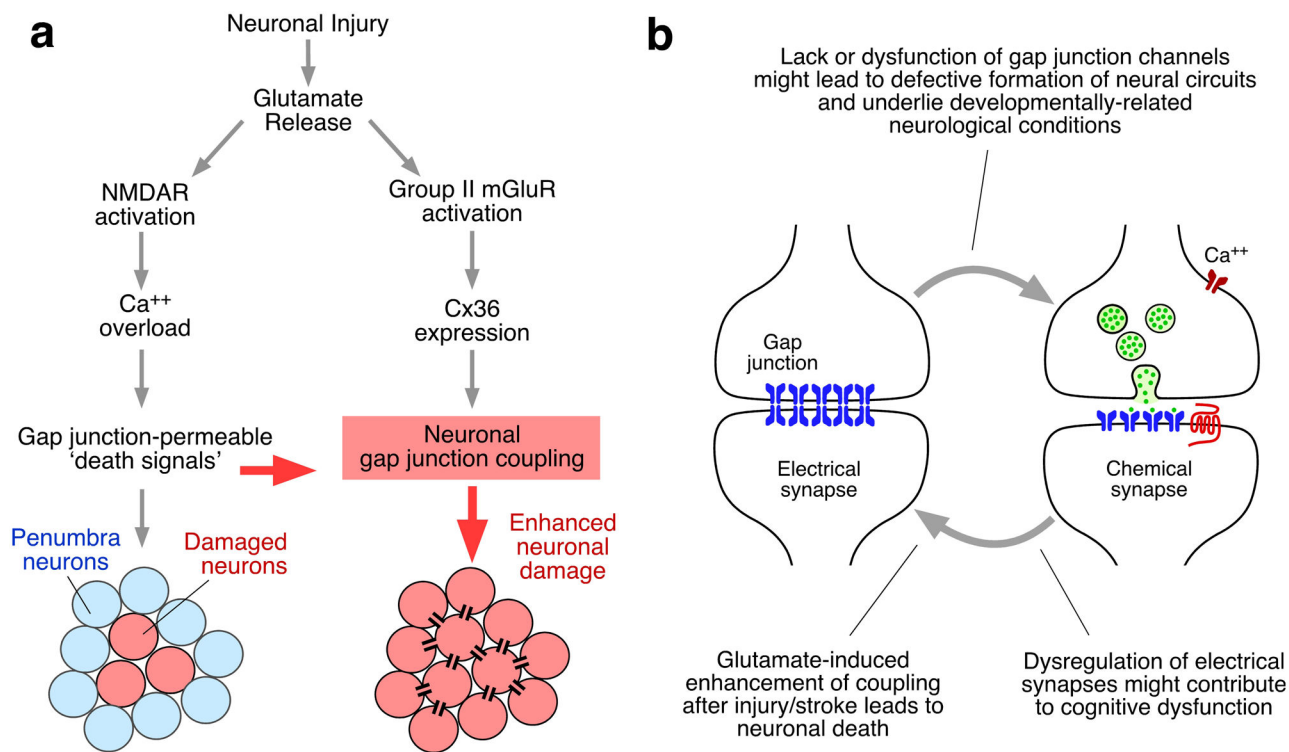
Figure 6. Interactions between chemical and electrical synapses and pathological processes
a, Chemical and electrical synapses interact after injury. Release of glutamate from injured neurons causes neuronal damage via NMDAR activation and Ca^{++} overload at the site of the lesion. Simultaneous enhancement of coupling via mGluR-dependent increased expression of Cx36 extends neuronal damage by facilitating the passage of 'death signals' to neurons adjacent to the lesion or "penumbra" area (from Belousov and Fontes et al., 2013). **b**, Summary of potential interactions of chemical and electrical synapses during pathological processes. The lack, or dysfunction, of gap junction channels at early developmental stages might lead to defective formation of critical neural circuits formed by chemical synapses, underlying developmentally-related neurological conditions. During adulthood, release of glutamate from compromised neurons after injury or stroke enhances coupling which leads to neuronal death in uncompromised areas adjacent to the lesion. Dysregulation of electrical synapses strength by neurotransmitters might contribute to cognitive disorders.