Functional contributions of electrical synapses in sensory and motor networks

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CrossMark

Intercellular interactions in the nervous system are mediated by two types of dedicated structural arrangements: electrical and chemical synapses. Several characteristics distinguish these two mechanisms of communication, such as speed, reliability and the fact that electrical synapses are, potentially, bidirectional. Given these properties, electrical synapses can subserve, in addition to synchrony, three main interrelated network functions: signal amplification, noise reduction and/or coincidence detection. Specific network motifs in sensory and motor systems of invertebrates and vertebrates illustrate how signal transmission through electrical junctions contributes to a complex processing of information.

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Introduction

Intercellular communication in the nervous system is mediated by two types of dedicated structural arrangements: electrical and chemical synapses. It is well documented that electrical synapses play a major role during development of the nervous system and that this intercellular communication, although to a smaller degree, persists in the adult nervous systems of invertebrates and vertebrates [1–3,4**,5,6]. Growing amount of data has established that electrical synapses play definite circuit functions in adult networks. This review focuses on specific network configurations at which electrical synapses play substantial physiological roles.

Structural properties of electrical synapses

While chemical synapses are asymmetric (pre and post-synaptic terminals have different components and

roles), electrical synapses exhibit a symmetric structure. Each one of the interconnected cells presents ionic channels that are aligned to channels in the other cell, forming a pathway for direct flow of current and small molecules (<1 kDa) from one cell to the other [7]. This intercellular communication is not particular of the nervous system as it is also present in the vast majority of animal tissues, and receives the generic name of gap junctions (GJs).

GJs play highly similar physiological roles in invertebrates and vertebrates and, consistently, bear highly similar structural characteristics. However, no homology was found between the proteins forming GJs in these two subphyla [8]. GJs are formed by innexins in the invertebrates [9] and by connexins in the vertebrates [10]. Twenty-five innexins have been identified in *C. elegans* [11], twenty one in leeches [12•] and nine in *Drosophila* [13]; four innexins were found in the nervous system of locust [14], and six in crabs [15]. In mammals twenty connexins have been characterized [16].

Innexin and connexin proteins exhibit four membrane-spanning regions. In vertebrates the three-dimensional structure of GJs has been extensively studied and the reports indicate that each hemichannel is a hexameric polypeptide [7]. A recent structural analysis performed in *C. elegans* found that each hemichannel in this nematode is an octameric polypeptide [17•]. It remains to be established if this is a particular case or a general property of invertebrate GJs.

Functional properties of electrical synapses

Several characteristics distinguish electrical and chemical synapses: (i) the delay between pre and postsynaptic signals is significantly shorter in electrical synapses; (ii) electrical synapses are more reliable than stochastic chemical synapse [18]; and (iii) electrical synapses are potentially symmetrical, where pre and postsynaptic sites are interchangeable, depending on which is the emitter (presynaptic) and which is the receiver (postsynaptic) at any instant.

GJs are considered and modeled as electrical resistors [19,20] and thus it is expected that transmission through electrical synapses is reproduced consistently upon repetitive stimulation. Because GJs are usually located at neuronal processes [21–23,24**], signal transmission is subjected to the characteristic low-pass filter imposed by their cable properties [25–28]. In turn, the amplitude

of the postsynaptic response is heavily dependent on the frequency components of the presynaptic signal.

In addition, the amplitude and dynamics of the transmitted signal is strongly influenced by the presence of voltage-activated conductances in the membrane associated with GJs [29[•],30[•],31].

Although potentially symmetrically bidirectional (ohmic), electrical synapses can also rectify: the conductance of GJs depends on the polarity of the transjunctional potential [the difference between the membrane potential (Vm) at each side of the GJ] [32]. This implies that, close to their resting potential, transmission of depolarizing or hyperpolarizing signals is transmitted better in one direction (e.g. cell A $\Rightarrow$ cell B) than in the other (cell B $\Rightarrow$ cell A) [33,34].

Rectification can be an intrinsic property of GJs, but it also can result from the differential intrinsic properties of the interconnected neurons [35[••]] or from coexistence of electrical and chemical synapses linking pairs of neurons [36,37].

Electrical synapses in the context of functional networks

In addition to fast transmission and synchronization, most recent research has taught us that electrical synapses can subserve three main interrelated network functions: signal amplification, noise reduction and/or coincidence detection. The following are examples where these functions are achieved in the context of sensory and motor networks.

Electrical synapses in sensory systems

Sensory systems are organized to maximize sensitivity and acuity. Lateral inhibition has been described as an important network mechanism, mediated mostly by chemical synapses, for increasing acuity [38,39], while lateral excitation has been proposed as a mechanism for increasing sensitivity. GJs are a common feature of lateral excitatory networks.

The connection between primary auditory afferents and the Mauthner cells, that command the startle reflex in teleosts, is mediated by electrical and chemical synapses (Figure 1a). The electrical connection shows a higher conduction in the antidromic than in the orthodromic direction, due to the asymmetry of input resistances between the coupled cells and the properties of the heterotypic junctions [35[••]]. It is proposed that upon stimulation of one auditory terminal, depolarization of the Mauthner cell can exert a fast retrograde depolarization of other afferents through the electrical synapses, amplifying the input to the command neuron.

A classical example of lateral excitation is found in the mechanosensory activation of the crayfish lateral giant neurons that command the tailflip escape response. The sensory neurons are interconnected by ohmic electrical synapses and are linked to the command neuron by rectifying electrical synapses (higher conductance when Vm$_{afferents}$ > Vm$_{command}$) (Figure 1b). This network was proposed as a mechanism to amplify the response within a restricted window of time, as inputs to a few afferents can instantaneously spread to others and increase the response of the command neuron [21,40,41]. An equivalent mechanism has been recently described in *C. elegans* [42,43] and in the mesencephalic nucleus of mammals [30[•]].

In the visual system of blowflies, a set of motion-sensitive (tangential) cells of the lobula plate process information in separate retinotopically arranged columns, and project to higher brain centers. Because neighbor tangential cells are electrically coupled (Figure 1c), each cell exhibits a broader receptive field than expected from the anatomy and connectivity of their respective dendritic trees [44,45]. Physiological and modeling studies indicate that this connectivity pattern confers the tangential cell population the capability of generating a linear integration of visual inputs [46] and the spread of signals through the electrical synapses exert a key role in this function [47].

The vertebrate retina is another classical example where lateral excitation between different types of neurons subserves amplification and improves signal-to-noise ratio. Photoreceptors are relatively noisy elements and their electrical coupling promotes a decrease of uncorrelated noise and a relative amplification of correlated visual signals, at the expense of certain degree of blurring [48]. Electrical synapses are not limited to the receptor layer but are vastly expressed among different neurons in the retina [49,50,51[••]].

In the olfactory system of insects, peripheral receptor neurons reach the antennal lobe, where they contact projection neurons that transmit excitatory signals to higher centers. Peripheral receptor neurons, expressing a specific odorant receptor, make chemical synapse with projection neurons in discrete regions of the antennal lobe called glomeruli. Projection neurons innervating the same glomerulus ('sister projection neurons') are linked by ohmic electrical synapses that provide for signal amplification [52] (Figure 1d).

In addition, projection neurons receive inputs from excitatory and inhibitory local interneurons that span across several glomeruli (Figure 1d). Excitatory interneurons and projection neurons are bidirectionally connected combining electrical and chemical synapse [52,53]. This horizontal pathway is interpreted as a mechanism to amplify and speed up odor detection at low odorant levels, at the expense of specificity. Additional interglomeruli interactions are mediated by a subset of inhibitory

Figure 1
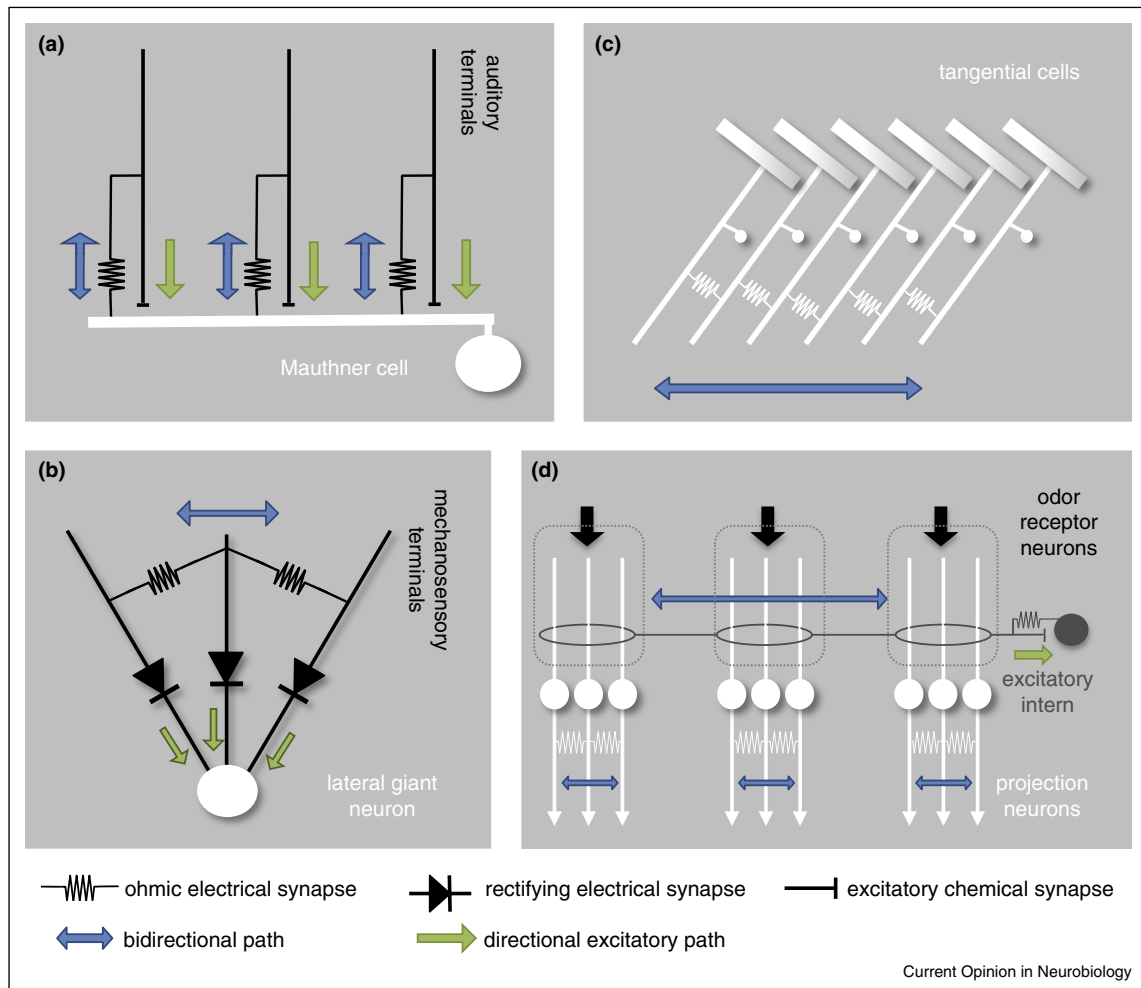
Schematic representations that highlight the role of electrical synapses in sensory systems. **(a)** Terminals from auditory neurons are connected to the Mauthner neuron in the goldfish brain through chemical and ohmic electrical synapses that allow bidirectional interactions; the size of the arrows indicate that the junctions exhibit a larger conductance in the antidromic direction [35••]. **(b)** Mechanosensory terminals are connected to lateral giant interneurons in the terminal ganglion of the crayfish nervous system through rectifying electrical synapses. In addition the mechanosensory neurons are interconnected by ohmic electrical synapses. **(c)** Tangential neurons extend their dendritic tree in the lobula plate of blowfly brains and are interconnected by ohmic electrical synapses located at their axons. **(d)** Specific odor receptor neurons contact projection neurons in specific glomeruli (represented as the rectangles delimited by pointed lines). Projection neurons innervating the same glomerulus are interconnected by ohmic electrical synapses. In addition, excitatory interneurons span several glomeruli and are connected to projection neurons by electrical and chemical synapses.

projection neurons that connect to uniglomerular projection neurons by chemical and electrical synapses, introducing another layer of horizontal interactions [54•].

The olfactory systems of vertebrates present several homologies with those of insects. Mitral cells (analogous to projection neurons) in the olfactory bulb receive inputs from receptor neurons and project the processed information to higher brain regions. Odor-specific mitral cells project to the same glomerulus, and are interconnected by electrical and chemical synapses that grant their synchronic firing [22,55]. Studies performed in zebrafish show that inhibitory interneurons in the olfactory bulb

are linked to mitral cells by electrical and chemical synapses modulating their activity in a bidirectional fashion. These synaptic interactions boost responses to weak stimuli and attenuate responses to strong stimuli. Boosting of weak inputs depends on electrical coupling, whereas attenuation of strong inputs is probably caused by chemical transmission [56••]. These network actions equalize the mean population response of mitral cells favoring a concentration-invariant identification of odors.

Electrical synapses in motor control

Motor behaviors are controlled by hierarchical systems. Higher levels determine global aspects of behaviors while

premotor networks at the lowest level are organized into distinct modules that configure sets of movements [57,58]. Studies at the premotor level established that electrical synapses subserve a variety of distinct functions.

In several invertebrate systems motoneurons (MNs) are interconnected by electrical synapses [15,59–61]. A similar picture was confirmed in the vertebrates [62]. Electrical coupling among MNs that innervate synergistic muscles [1] can be simply interpreted: synchronic activation of MNs can grant a more precise coactivation of muscles. However, electrical synapses could be expressed among MNs that do not (always) fire in synchrony [36,37].

A particular example in the leech nervous system is the bilateral pair of electrically coupled MNs that control the activity of the pair of heart tubes. In line with the asymmetric activity of the heart tubes, these MNs receive asynchronic rhythmic input [63]. Experimental and modeling work suggests that the electrical synapses influence both the intersegmental delay and the side-to-side phase difference throughout their rhythmic activity [64].

In several invertebrate systems it was observed that MNs are not mere output units of the central nervous system but form active part of networks that control rhythmic motor behaviors. Classical and extensively discussed examples are the pyloric rhythm of the crab digestive system and the leech swimming where MNs form part of the oscillatory networks and are linked to other units in the circuit by chemical and electrical synapses [65,66]. More recently a similar picture was uncovered in the zebrafish, where MNs are electrically coupled to excitatory interneurons that are part of the swimming motor pattern [67•].

Swimming in molluscs is controlled by a set of four interneurons linked by reciprocal inhibitory chemical synapse and ohmic electrical synapses [68,69].

C. elegans exhibits rhythmic undulatory forward and backward locomotion. The direction of movement is determined by interactions between specific forward and backward motor circuits. Backward premotor neurons are linked to specific backward MNs by chemical and electrical synapses; a similar connectivity was found for the forward circuit (Figure 2a). In spite of the apparent symmetry, a series of studies determined that electrical synapses in the backward network, but not in the forward one, play a key role in regulating forward movement [70]. GJs function as shunts that decrease the excitability of the premotor neurons that control backward MNs, establishing a bias for a higher forward output.

As mentioned earlier, MNs can be electrically coupled, promoting co-activity of different muscles. However,

Figure 2

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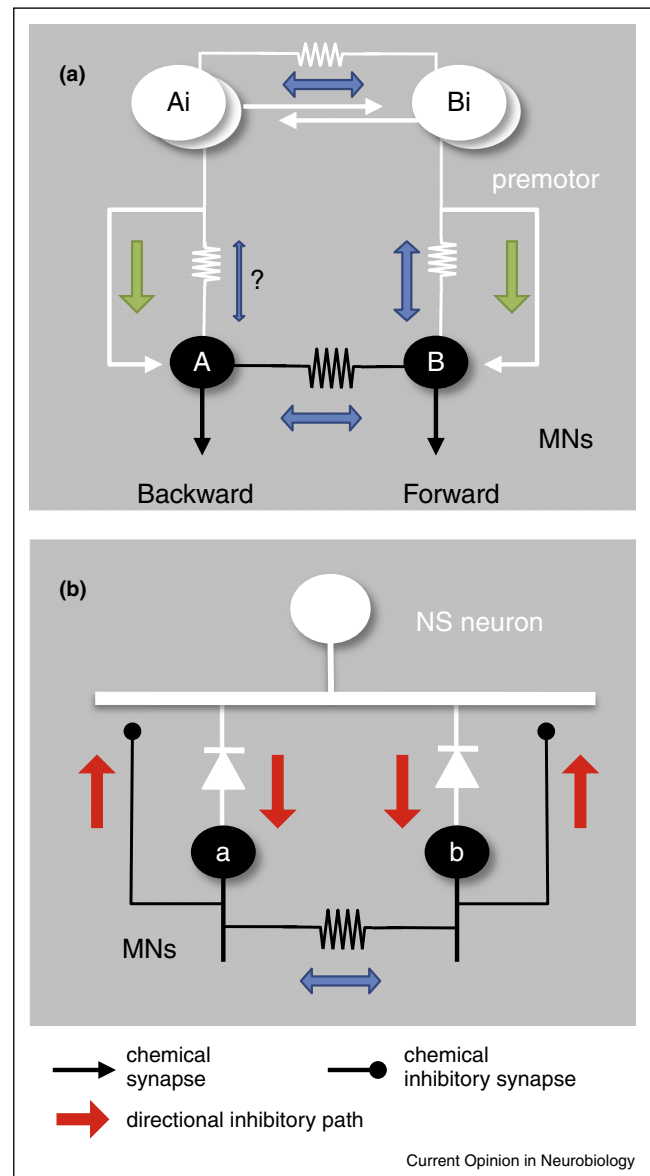
Schematic representations that highlight the role of electrical synapses in motor systems. **(a)**. In *C. elegans* interneurons AVA and AVE (summarized as Ai) control MN A that produces backward movement, and interneurons PVC and AVB (summarized as Bi) control MN B that produces forward movement. Interneurons and MN are linked by chemical and electrical synapses. Interneurons are also interconnected by mixed synapses and MNs are interconnected by electrical synapses. **(b)** In the midbody ganglion of leeches the NS neuron is linked to MNs by rectifying electrical synapses and MNs produce chemically-mediated inhibitory responses (polysynaptic) onto NS. MNs are linked among themselves by relatively ohmic electrical synapses. Note that most of the symbols are denoted in Figure 1.

muscle groups that function synergistically in one behavior could act out of phase in another, and therefore coupling requires a fast control mechanism. A circuitry was described in the nervous system of the leech where

non-synergistic MNs are widely coupled by ohmic electrical synapses. The mechanism is centered on a pair of premotor nonspiking (NS) neurons that are linked to every excitatory MN by chemical and rectifying electrical synapses (Figure 2b): activation of MNs evokes a hyperpolarizing response in NS mediated by chemical synapse; the electrical synapses are active when $Vm_{NS} < Vm_{MN}$. As a consequence of this network the MN–MN interactions are counteracted [36,37]. For example, activation of MN-a shown in Figure 2b will cause a direct excitatory signal onto MN-b through the ohmic electrical synapses that link them, and an inhibitory signal via NS. Depolarization spreads from the MN to NS through the rectifying electrical synapses but the chemically mediated inhibition prevails, and therefore the effective signal transmitted to the other MNs via NS is inhibitory. The two opposite signals cancel each other and no net change in Vm_{MN-b} is observed, masking the electrical coupling between the MNs. In general terms the network was proposed to function as a recurrent inhibitory network [71••] and it was found effective when the nervous system displays a rhythmic motor pattern compatible with crawling [72].

Conclusions

Electrical synapses are fast means of communication that blur the cellular boundaries, generating fast and reliable routes of communication between neurons that are individual processing units. The sensory and motor networks described here illustrate circuitry motifs in which electrical synapses provide, mostly, means of amplification. But as described in the *C. elegans* and leech nervous systems, given particular network configurations, it can serve as a fast and reliable inhibitory mechanism. The level of GJs expression can be modulated in different physiological conditions, but while present in a circuitry, exerts a variety of robust effects.

Conflict of interest

Nothing declared.

Acknowledgments

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This review summarizes a mechanism of recurrent inhibition uncovered in the leech nervous system and relates it to what has been described in vertebrates. The leech network is centered on a pair of nonspiking neurons that are linked to every excitatory motoneuron in the leech via chemical and electrical synapses. This network achieves two major effects: uncouples motoneurons linked by electrical synapses and controls the general level of motor activity throughout specific motor patterns.

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