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Electrical transmission: two structures, same functions?

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Abstract

Electrical synapses are finding increasing representation and importance in our understanding of signaling in the nervous system. In contrast to chemical synapses, at which molecules are evolutionary conserved, vertebrate and invertebrate electrical synapses represent molecularly different structures that share a common communicating strategy that allows them to serve very similar functions. A better understanding of differences and commonalities regarding the structure, function and regulation of vertebrate and invertebrate electrical synapses will lead to a better understanding of the properties and functional diversity of this modality of synaptic communication.

Keywords

Gap junction; Connexin; Innexin; Development; Function; Plasticity

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Transfer of information between neurons is accomplished via at least two main modalities of communication, chemical and electrical transmission. Chemical transmission involves depolarization-evoked (often but not always by an action potential) release of a neurotransmitter from one of the interacting cells which, by binding to one or more specific receptors in a second cell, alters its membrane potential and/or activates cytoplasmic biochemical signaling cascades. This mechanism was the first one to be identified during the search for the nature of synaptic transmission (Fatt, 1954), leading to the impression that chemical transmission constituted the main or perhaps only modality of interneuronal communication. However, physiological analysis of the properties of other putative synaptic contacts led to the demonstration that neurons can additionally communicate with each other electrically, via what seemed to be intercellular pathways of low electrical resistance. The early seminal studies in crayfish by Furshpan and Potter (1959) demonstrated that changes in the membrane potential in one cell can evoke corresponding changes in the membrane potential of a second cell, suggesting that at some junctions electrical currents can directly spread between cells. Transmission was in this case directional, polarized and voltage-dependent (rectifying), indicating the electrical nature of this then novel modality of communication (Furshpan and Potter, 1959). This “electrotonic” type of transmission was subsequently identified in fish (Bennett et al., 1959; Furshpan, 1964), birds (Martin and Pilar, 1963) and mammals (Baker and Llinás, 1971), revealing the ubiquitous presence of this modality of communication in both vertebrate and invertebrate nervous systems.

Early investigations in fish led to the observation that electrical transmission was correlated with areas of close membrane apposition between the connected cells, as visualized by electron microscopy (Bennett et al., 1963; Robertson, 1963; Robertson et al., 1963; Furshpan, 1964), thus contributing to the identification of the structural basis of electrical transmission: the gap junction. Such association was found as well in other cases at which electrical transmission was present, including invertebrates (Peracchia, 1973; Hanna et al., 1978). Gap junctions are aggregates of tightly clustered intercellular channels (each formed by the apposition and binding of two multimeric structures, or "hemichannels") that bridge the interiors of two neighboring cells (Goodenough and Paul, 2009). These junctions were later found to be present in most tissues and cell types, suggesting that in addition to serving as pathways of low resistance for electrical currents between cells of excitable tissues (i.e., nervous system and heart) they also provide a means for the exchange of small signaling molecules more generally between all types of cells (Goodenough and Paul, 2009). Thus, the search of the mechanism underlying electrical synaptic communication is tightly linked to the identification of the widespread intercellular junctions we now recognize as gap junctions.

It is now well established that both vertebrate and invertebrate gap junctions mediate electrical and metabolic coupling. More recent evidence has also shown that gap junctions play roles in the initiation of the formation of neural circuits during development, and that their assembled proteins can act as selective adhesion molecules and function as hemichannels that support extracellular chemical signaling. Despite serving in a range of similar functions, vertebrate and invertebrate gap junctions are comprised of molecularly different (Herve et al., 2005) but topologically similar structures that form channels (Figure 1) with different conductance and permeability. Although sharing remarkably similar transmembrane topologies (4 transmembrane domains, cytoplasmic C- and N-termini), vertebrate connexin and invertebrate innexin gap junction channel-forming proteins have unrelated amino-acid sequences (Herve et al., 2005; Phelan, 2005). Although in both cases individual channels aggregate into clusters to form gap junctions, structural differences differentiate vertebrate and invertebrate gap junctions, including different hemichannel structure (hexamers in connexins vs. both hexamers and octamers in innexins), inter-channel distance and regularity, and membrane separation (Skerrett and Williams, this issue). Moreover, in contrast to connexin based gap junctions, at which channel particles appear in the P-face of freeze-fracture replicas, they appear in the E-face at innexin-based gap junctions (Figure 1) (Peracchia, 1973; Hanna et al., 1978; Shivers and McVicar, 1995), suggesting that not only are the channel-forming proteins different, but their supportive scaffolds might be organized differently and likely include different associated molecules. Thus, while both vertebrate and invertebrate gap junctions converge on remarkably similar functions, the fact that they consist of different molecular structures raises the possibility they could have additional functions that are exclusive for each type. While the existence of type-specific functions is at this point merely speculative, a deeper understanding of their individual molecular and structural complexity could help to expose unsuspected properties of these two types of electrical synapses.

In the past few years, there has been a very dramatic increase in interest in the structural and functional properties of electrical synapses, as well as their roles in neural development and

their contributions to the neural connectome. This issue of Developmental Neurobiology provides a window into some key current developments in the field, combining and comparing acquired knowledge from both connexin-based and innexin-based electrical synapses. Appropriately, the first article of this issue (Skerrett and Williams, this issue) reviews our current knowledge of gap junction channels comprised of invertebrate innexins or vertebrate connexins. By comparing them at both structural and biophysical levels, Skerret and Williams provide a greater appreciation of gap junctional communication in general. The second contribution focuses on a recently discovered zebrafish connexin (Cx79.8), which was initially identified in the lens but is now known to be expressed in retinal, cerebellar and a few other neurons as well (Yoshikawa et al., this issue). As with other neuronal connexins, communication via Cx79.8-based electrical synapses seems to be regulated by phosphorylation. Interestingly, teleosts, and zebrafish in particular, are characterized by the significant diversity of connexins that comprise their electrical synapses, in marked contrast to the small number of connexins (mostly Cx36) known to be expressed by mammalian neurons. Electrical synapses are often perceived as just simple clusters of intercellular channels that lack sophisticated properties. However, a wealth of evidence indicates that electrical synapses are both functionally and structurally complex and require the contribution of multiple proteins, not just those forming channels. Beyond complexities in the molecular composition of the gap junction channels, the third article (Miller and Pereda, this issue) reviews and discusses the structural complexity of electrical synapses and how this complexity might be the source of their functional diversity.

Beyond conductive functions (electrical and metabolic coupling), an increasing amount of evidence in both vertebrates and invertebrates suggests that electrical synapses can also act as adhesion and recognition factors during the development of the nervous system and contribute to sculpting neuronal morphology and their pattern of synaptic connections within a network. These properties are the topic of another review article (Baker and Macagno, this issue), which highlights evidence obtained in three different experimental preparations (*C. elegans*, medicinal leech and fly) that express multiple neuronal innexins. The possible roles of different innexin genes in controlling these developmental processes have been assayed by mutation and ectopic expression in identified neurons in these species. In the leech nervous system, identified neurons have been shown to express different subsets of innexins, supporting the hypothesis that multiple innexins can function as recognition factors in the formation of specific synaptic circuits. Ectopic expression of single innexins can lead to the expressing neuron joining different circuits (Firme et al., 2012). While electrical junctions can and do undertake similar roles in different organisms, they can also be widely diverse in function and structure in the same organism. This is the case in *C. elegans*, which despite the small number of neurons (302) and cells in general, exhibits a strikingly large number of innexins genes (25 genes). The diversity and contributions to development and behavioral phenotypes of innexin genes in C. elegans is the topic of another article (Hall, this issue). As in the leech, some cells can express multiple innexins, a property that leads to the formation of various gap junction configurations. Moreover, due to their widespread distribution, gap junctions significantly contribute to the connectome (interneuronal synaptic wiring) of this organism.

After dealing with the molecular, structural and developmental roles of electrical synapses, a series of papers deal with the impact of electrical coupling in networks of electrically connected neurons. Electrical coupling mediated by electrical synapses can generate non-intuitive circuit dynamics, as evidenced by experimental and computational models inspired in the connectivity of the crustacean stomatogastric ganglion (Marder et al., this issue). This article discusses how information can travel via parallel mono- and polysynaptic pathways formed by electrically coupled neurons to generate ambiguities in the interpretation of electrophysiological recordings. Rectifying properties of gap junction channels, which endow directionality to synaptic transmission, can greatly contribute as well to the generation of these variable network dynamics. The impact of electrical coupling mediated by electrical synapses in the mammalian CNS is considered next (Connors, this issue). While synchronization of ensembles of neurons is perhaps the most recognizable property of electrical transmission, electrical synapses are also capable (amongst other properties) of producing inhibition, promoting desynchronization and acting as coincidence detectors. In addition to these properties, electrical synapses are highly dynamic and their conductance is highly regulated, adding yet another layer of complexity to their impact on neural networks. Together with the actions of neurotransmitter modulators such as serotonin, dopamine and noradrenaline, electrical synapses are greatly influenced by the activity of nearby glutamatergic synapses, endowing them with activity-dependent potentiation. Electrical synapses between inferior olivary cells are one of these examples, at which the action of NMDA receptors localized in the vicinity of gap junctions leads to enhancement of electrical coupling between these neurons. The article by Yang et al. (Yang et al, this issue) further explores the functional consequences of NMDA-dependent modulation using light stimulation in inferior olivary cells expressing channel rhodopsin. Optical activation of a single cell travels via polysynaptic pathways formed by electrical synapses to produce depolarization in cells remotely located and this depolarization was enhanced in most of the examples examined by activation of NMDA receptors. Thus, this set of papers demonstrate how electrical synapses are capable of contributing to network dynamics in many ways.

In the brain, gap junctions are not restricted to neurons but are also present in glia, which express a wide variety of connexins. Moreover, the function of both connexin and innexin made channels are not restricted to the intercellular channel configuration (docking of two hemichannels or “connexons”) but can also play functional roles as hemichannels. In vertebrates, a second family of channel forming proteins related to innexins, the pannexins, has been shown to function as hemichannels. Glia actively contribute to a number of critical physiological functions, including the response to a number of pathological processes. It was previously shown that exposure to high levels of glucocorticoids during early life is capable of leading to long-lasting neuroinflamation involving the activation of microglia and astrocytes. The report by Maturana et al. (Maturana et al., this issue) shows that this response also involves the contribution of oligodendrocytes and requires the action of pannexin 1 and connexin hemichannels, which activity is enhanced under these conditions. The inflammatory process could contribute to demyelinating diseases associated with exposure to glucocorticoids during early stages of life. Finally, beyond their function in the brain, the last article (Mathews and Levin, this issue) deals with a more general role of gap junctions. The article discusses the contribution of gap junctions to the generation of large-

scale anatomical patterns by dynamically regulating the topology of bioelectric networks. By reviewing examples ranging from the growth of zebrafish fin to head-tail polarity and regeneration in planarian, the authors argue that the dynamic characteristics of neural networks are likely to apply to gap junction communication in non-neural tissues.

We hope this set of articles serves as a platform for a deeper appreciation of the molecular and structural diversity of neuronal gap junctions and the diverse functional contexts to which their functions critically contribute, generating enthusiasm for expanding our understanding of these two fascinating structures.

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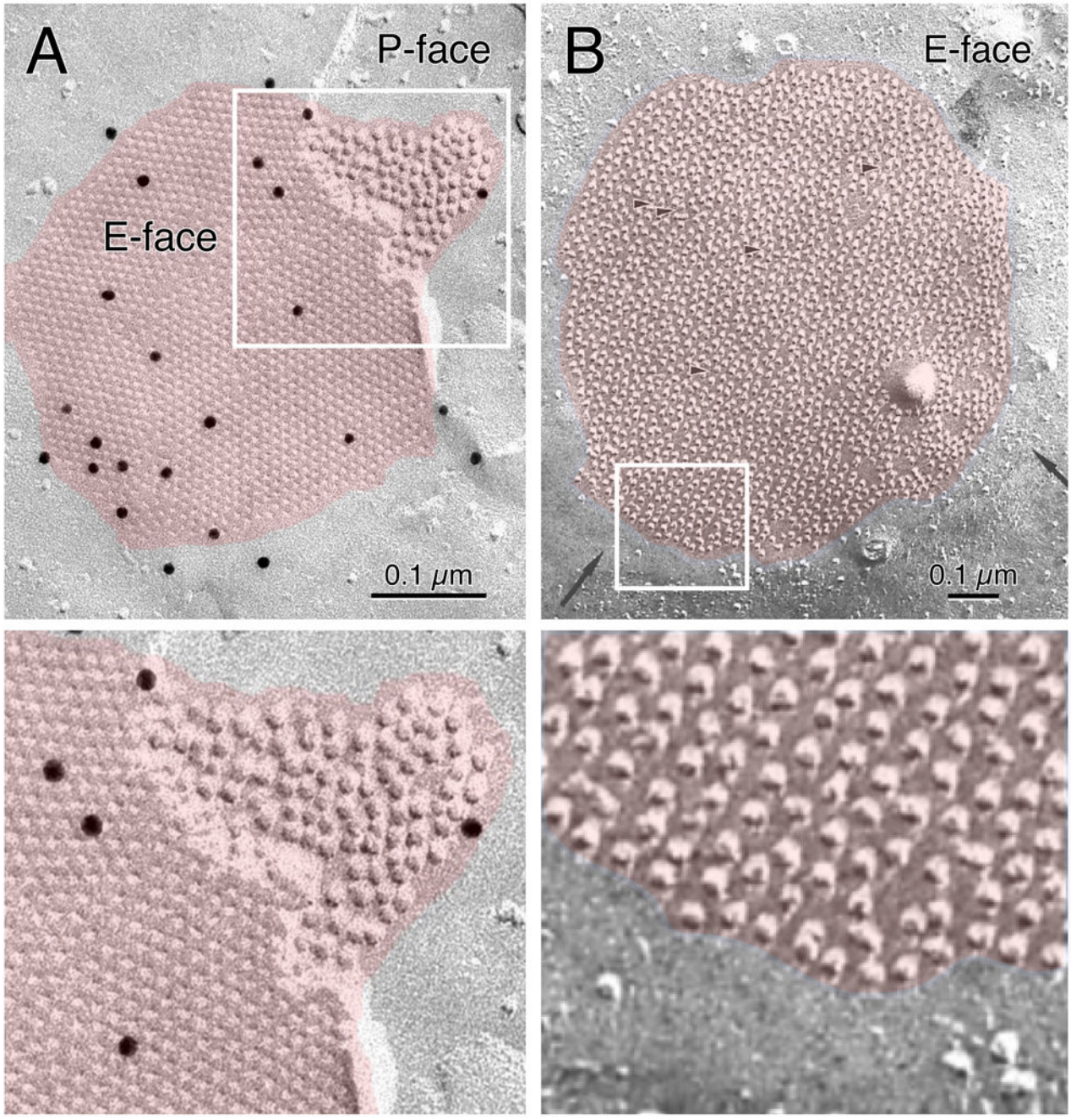

Figure 1. Structure of connexin and innexin based gap junctions

A, Freeze fracture immunogold labeling of a gap junction (pink overlay) between a large Myelinated Club ending and a Mauthner cell in goldfish. Both e-face pits and p-face particles can be observed. Immunogold indicates labeling with an anti-Cx36 antibody, which recognizes Cx36-like connexins in fish. Modified from Pereda et al., 2003 (Pereda et al., 2003), with permission. *B*, Freeze fracture image of a gap junction (pink overlay) between the lateral giant axon and the giant motor fiber of a crayfish, at which e-face particles can be observed. Modified from Hanna et al, 1978, with permission (Hanna et al., 1978). Lower

panels are magnified images of the areas boxed in panels A and B. Note differences in size and the distance. Intramembrane particles are generally observed in the P-face in connexin based gap junctions (A) whereas they adhere to the E-face in the innexin based junctions (B). Please note that panel B is about half the magnification of panel A. so that the spacing and intramembrane particles between both junctions. For comparison of spacing and size of intramembrane particles between both junctions, lower panels are displayed at the same magnification (note difference in box size).