



Gap junctional coupling in the vertebrate retina: Variations on one theme?

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ABSTRACT

Gap junctions connect cells in the bodies of all multicellular organisms, forming either homologous or heterologous (i.e. established between identical or different cell types, respectively) cell-to-cell contacts by utilizing identical (homotypic) or different (heterotypic) connexin protein subunits. Gap junctions in the nervous system serve electrical signaling between neurons, thus they are also called electrical synapses. Such electrical synapses are particularly abundant in the vertebrate retina where they are specialized to form links between neurons as well as glial cells. In this article, we summarize recent findings on retinal cell-to-cell coupling in different vertebrates and identify general features in the light of the evergrowing body of data. In particular, we describe and discuss tracer coupling patterns, connexin proteins, junctional conductances and modulatory processes. This multispecies comparison serves to point out that most features are remarkably conserved across the vertebrate classes, including (i) the cell types connected via electrical synapses; (ii) the connexin makeup and the conductance of each cell-to-cell contact; (iii) the probable function of each gap junction in retinal circuitry; (iv) the fact that gap junctions underlie both electrical and/or tracer coupling between glial cells. These pan-vertebrate features thus demonstrate that retinal gap junctions have changed little during the over 500 million years of vertebrate evolution. Therefore, the fundamental architecture of electrically coupled retinal circuits seems as old as the retina itself, indicating that gap junctions deeply incorporated in retinal wiring from the very beginning of the eye formation of vertebrates. In addition to hard wiring provided by fast synaptic transmitter-releasing neurons and soft wiring contributed by peptidergic, aminergic and purinergic systems, electrical coupling may serve as the 'skeleton' of lateral processing, enabling important functions such as signal averaging and synchronization.

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1. Introduction

Across the animal kingdom, two major forms of interneuronal communication are utilized. Chemical synaptic transmission is the numerically dominant mode of signal transmission. In this mode, the excited (pre-synaptic) neurons release chemical substances (transmitters, neuromodulators) that bind to receptor molecules on the plasma membrane of the targets (post-synaptic neurons). These receptors are highly selective for the appropriate transmitter, which in turn gate the excitation, inhibition or modulation of the post-synaptic neurons.

The other form of inter-neuronal signal transmission is mediated by so-called electrical synapses or gap junctions. Gap junctions are molecular bridges between cells that provide low resistance avenues for electrical and/or metabolic communication of coupled cells. Gap junctions were described by electron microscopy over 50 years ago in peripheral tissues (skin: Farquhar and Palade, 1965, muscle: Rosenbluth, 1965) and in the brain (Watanabe, 1958; Brightman and Reese, 1969). Similar to chemical synapses, membrane surfaces of electrical synapse forming cells make close membrane appositions. However, the synaptic gap is some ten times narrower in the case of electrical synapses (1–2 nm), a characteristic feature that inspired Goodenough and Revel (1970) to dub them gap junctions. At the site of electrical synapses, plasma membranes are anchored to the cytoskeletal matrix via a zonula-occludens complex (Rash et al., 2004; Ciolofan et al., 2007; Li et al., 2004a,b, 2008) and protein based structures span both cell membranes. These join to form continuous tunnels permeable to several ions and small molecules (<1 kDa). The tunnel is created by aligned connexon halves (hemichannels), one inserted into each apposing membrane. Connexons are oligomerized from six connexin subunits that are members of a multigene family with relatively conservative molecular structure. All described connexins have four transmembrane domains, two extracellular and an intracellular loop with the C- and N- termini in the cytoplasm. Various cells may express different connexin subunits to form gap junctions depending on the function served.

Although the existence of electrical synapses has long been known (Furshpan and Potter, 1957; Watanabe, 1958) they seemed less prevalent, thus thought to be inferior in the nervous system. However, this dogmatic view has been challenged in the past two decades and it is now clear that electrical synapses are ubiquitous elements of the nervous system. The discovery of highly specific antibodies and the introduction of transgenic animal lines triggered a surge of experimental work that lead to the identification of the molecular building blocks of gap junctions, the connexin proteins.

Gap junctions have been recognized as significant components of the retinal circuitry almost 40 years ago (Raviola and Gilula, 1973). Most of them mediate lateral signaling by coupling similar

retinal neurons into extended, planar arrays and sometimes they also transmit signals vertically between different cell types (Cook and Becker, 1995). Retinal gap junctions are of a particular interest to neuroscientists, since there is no other area in the nervous system where gap junctions are found in such a great quantity and participate so extensively in signal processing. A number of recent reviews have surveyed the electrical and/or network properties, tracer coupling and cell-to-cell connections of retinal gap junctions (e.g. Bloomfield and Völgyi, 2009; Cook and Becker, 2009; Demb and Pugh, 2002; Roerig and Feller, 2000; Söhl et al., 2000; Vaney and Weiler, 2000; Weiler et al., 2000). However, the phylogenetic aspects and/or conservation of these properties have not been reviewed for over 15 years since the seminal work of Cook and Becker (1995). Yet a lot of new evidence has been presented since then, just to mention the characterization of gap junction forming connexin subunits in many retinal contacts. Given that the connexin amino acid sequences (and the coding DNA nucleotide sequences, for that matter) have great potential to reveal new phylogenetic and functional aspects, we will provide a multiple species comparison of the vertebrate retinal gap junctions.

2. Aims

In this review, we blend old dogmas with recent advances in neurobiology with regard to retinal gap junctions in key neuronal circuits. To this end, we will provide a comprehensive overview on retinal gap junctions in vertebrate species and survey interspecies differences and similarities of: (i) the cell types connected with gap junctions, (ii) the connexin composition of individual junctions, (iii) the way gap junctional conductivity relates to function and (iv) the modulatory processes that influence the junctional properties. Finally, we will use the acquired data to make conjectures both about the evolution of the retinal electrical wiring and the possible origin of connexin divergence.

3. Gap junction protein families and retinal gap junction proteins in vertebrates

Intercellular channels resembling gap junctions exist in many lower multicellular organisms, but connexins and their genes have only been identified in deuterostomes (Willecke et al., 2002). It has been suggested that the connexin gene family has developed through duplication of ancestral connexin gene(s) (Bennett et al., 1991). In the best-known mammalian genomes (mouse and human), approximately 20 connexin genes were sequenced (Söhl and Willecke, 2003). However, there have been more connexin genes identified in fish species than in mammals (Cruciani and Mikalsen, 2006), therefore it is sometimes difficult to categorize the numerous connexin orthologs (similar connexins of different species) and

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